DESIGN AND STUDY OF A DRUG DELIVERY SYSTEM COMPRISING COMPACTED POLYMER-COATED PELLETS

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DEDICATION

This thesis is dedicated to all

who made it possible

DESIGN AND STUDY OF A DRUG DELIVERY SYSTEM COMPRISING COMPACTED POLYMER-COATED PELLETS

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ABSTRACT

Due to the physical limitations associated with the size of a hard gelatin capsule shell it has not been feasible in practice to present a low potency drug in the form of a sustained release multiparticulate delivery system. The aim of this work was to design a tablet which, on oral administration, rapidly releases intact polymer coated pellets in which the integrity of the cores and the release retarding membrane is preserved.

A comprehensive study is made of the effect of uncoated pellet formulation and pelletization processing variables on the physical, skeletal and tensile properties of uncoated pellets. Investigation into the effect of the drying technique on the properties of uncoated pellets is also reported. This work has shown that the aqueous solubility of pellet components and the drying technique used has a marked effect on pellet diametral strength, elasticity, surface characteristics and *in-vitro* drug release.

Pellets were coated using aqueous dispersions of polymethacrylate, ethylcellulose and silicone elastomer polymers. The effect of the film composition on tensile properties was studied by evaluating the mechanical properties of free-films using the technique of indentation hardness testing. The quality of the film coating and the effect of polymer loading was evaluated using *in-vitro* dissolution testing and by scanning electron microscopy. It was found that those polymeric film formulations whose tensile properties most resembled the tensile properties of the pellet cores resulted in films which were best able to withstand the applied stress associated with pellet compaction. Those films exhibiting significantly greater elasticity than the uncoated cores resulted in pellets which exhibited a tendency for instantaneous elastic recovery on removal of the applied load; tablet formation was therefore prohibited.

Polymer coated pellets were successfully compacted into tablets with an inert direct compression blend comprising large particle size grades of lactose and microcrystalline cellulose. Pellet distribution within the tablet matrix (evaluated by image analysis of tablet sections, microphotography and uniformity of content data) failed to show evidence of particle segregation. Comparative *in-vitro* release profiles of compacted and non-compacted pellets shows that some physical damage is being caused to pellets as a result of the compaction process.

Pellets are rapidly released from the matrix on disintegration of the tablet. Visual observation of released pellets indicated that they were intact, however microscopic examination revealed evidence of impaired surface quality. Pellet damage during compaction appears to be independent of the magnitude of the applied load and fracture of the polymer coating is restricted to those pellets in contact with the surfaces of the punches and die during tableting.

" This is not the end. It is not even the beginning of the end. But it is perhaps, the end of the beginning "

Winston L. S. Churchill, 1942.

" Writing a book is an adventure. To begin with, it is a toy and an amusement; then it becomes a mistress, and then it becomes a master, and then a tyrant. The last phase is that just as you are about to be reconciled to your servitude, you kill the monster, and fling him out to the public "

Winston L. S. Churchill, 1949.

" Where observation is concerned, chance favours only the prepared mind "

Louis Pasteur, 1854.

PRESENTATIONS

A part of the work described in this thesis has been presented in the following

i). DYER A.M., KHAN K.A. and AULTON M.E.

Consequence of drying method on the physical and release properties of pellets of ibuprofen and lactose.

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CHAPTER 1

GENERAL INTRODUCTION

The approach to sustained drug delivery described in this study involves the design and study of a rapidly disintegrating single-unit system comprising compacted polymer-coated multiparticulates.

The presentation of polymer coated particles enclosed in a hard gelatin capsule is a popular delivery system in which the dangers of dose dumping and ineffective blood levels are avoided by distribution of the dose in multiple-units. It is recognised that a multiple-unit sustained release dosage form presents a highly preferable alternative to a single-unit system for oral administration (Davis et al. 1984). However due to the physical limitations associated with the size of a hard gelatin capsule shell it has not been possible to administer a medium- to high-dose drug in the form of a sustained release multi-particulate delivery system. The aim of this work therefore was the design and study of a tablet dosage form which on oral administration rapidly releases intact polymer coated pellets with the integrity of pellet cores and the release retarding membrane being preserved.

Advantages associated with sustained release delivery systems include the need for less frequent dosage administration, a prolongation of drug absorption and a reduction in peak plasma drug concentrations; this results in an overall increase in the therapeutic effect for any given dose of drug. Furthermore there is improved patient compliance and a reduction in unwanted side effects which may be associated with high peak plasma drug concentrations. Also for a multiparticulate system, it may be possible to reduce rapid delivery of an irritant drug to localised parts of the gut mucosa.

The pharmacological advantages of multiparticulate sustained release delivery systems are numerous. Bechgaard and Nielsen (1978) reported that a multiple-unit dosage form presents a highly preferable alternative to the single-unit devices due to greater predictability and reproducibility of the therapeutic effect and a reduced risk of side

effects. These authors report that a monolithic sustained release delivery device is unable to reach the small intestine (the primary site of drug absorption) independently of gastric emptying.

Gastric emptying is a function of many variables including the degree of distension of the stomach, the composition and viscosity of the stomach contents and pH, in addition to being subject to neural and hormonal control. The application of multiparticulates to sustained drug delivery systems essentially eliminates the dependence of the drug effect on gastric emptying since particles of diameter approximating 1mm are sufficiently small to pass through the pylorus between sphincter openings (Bechgaard and Nielsen 1978). This facilitates reproducible transport of drug to the optimum site of absorption; it avoids high local concentrations of drug since the multiparticulates are distributed over a larger surface area which in turn minimises the risk of local irritation of the gut mucosa. The transport of sub-units is largely independent of the presence and the nature of food in the stomach and the variation in the bioavailability of multiple-unit dosage forms is therefore less subject to variation in both gastric-emptying and intestinal transit time.

Davi et al. (1984) discuss how the stomach handles solid objects greater than 2mm diameter in a different manner to smaller particles and emphasise the importance of the time the dosage form remains in the stomach in respect of product bioavailability. Ganderton (1985) discussed the advantages associated with a drug contained in several hundred particles compared with a monolithic system and how any occlusion by the gut contents of the dosage form will only affect a small proportion of the dose of a multiple-unit system as opposed to the entire dose for a monolithic delivery device.

Scope of this thesis.

In this present work pellet formulations containing high percentages of the low potency drug ibuprofen were studied and manufactured using the technique of extrusion and spheronisation. Detailed consideration was given to the effect of formulation and manufacturing variables on the physical characteristics and release properties of pellets. The materials of uncoated pellet formulations must possess the inherent cohesive and plastic properties necessary for the formation of good quality extrudate suitable for spheronisation. A study of the technique of pelletization enabled the formation of spherical particles containing high concentrations of drug with regular shape, uniform size and smooth surface characteristics ideal for the application of a release retarding film coating.

It is widely accepted that many pelletization processing variables are capable of influencing the fundamental properties of uncoated pellets. However a major objective of this present work was to elucidate the effect of the drying technique on the mechanical properties and surface appearance of spheronised particles. Much work has been reported on the effect of the formulation variables and processing variables associated with extrusion and spheronisation, but little attention has been paid to the nature and length of the drying process. This work has revealed that the drying technique employed as a pelletization unit process has a quantifiable effect on the diametral strength and elasticity of pellets, the *in-vitro* drug release and the surface characteristics of ibuprofen pellets.

Sustained drug release was achieved by the application of a release retarding membrane to the pellets by the use of an aqueous polymeric dispersion. Film coating was performed using a fluidised bed apparatus. A comprehensive study was made of the effect of the nature of the polymer and formulation variables on the quality of the resultant film and its

suitability for use as a release retarding membrane for multi-particulates, which by design must be able to withstand the stress associated with pellet compaction into a tablet matrix. Free-films comprising polymer systems of the polymethacrylates, ethylcellulose and silicone elastomer were prepared using a rotating polytetrafluoroethylene (PTFE) cylinder and the mechanical properties evaluated using the technique of indentation hardness.

The tensile properties of both uncoated and coated ibuprofen pellets and placebo pellets were studied using a Single Particle Crushing Assembly. Particular importance was placed on elucidating the relative elasticities of pellet formulations and their diametral strengths; these pellet formulations were required to withstand the applied stress associated with the compaction process. The fundamental bonding forces determining the strength of pellets as a consequence of the pelletization process are discussed.

Drug release from uncoated and coated pellets was evaluated using *in-vitro* dissolution testing. The use of this diagnostic technique enabled a study to be made of the effect of the nature of the polymer, polymer loading, formulation variables and the overall film quality on the drug release mechanism(s) from coated pellets. Qualitative film evaluation was made using scanning electron microscopy.

Tablet compression involved designing an inert direct compression diluent blend suitable for compaction with the polymer coated pellets. This blend was designed to enable the formation of a mechanically strong tablet which rapidly disintegrated *in vitro* yielding intact pellets. Tablet formulations composed of compacted polymer coated pellets containing 800mg ibuprofen are studied. The particle size of the excipients of the diluent blend and their relative proportions were carefully optimised. The minimum quantity of diluent necessary to fill the void volume within a tablet comprising compacted polymer coated

spheres was elucidated in order that the integrity of the pellets could be maintained and a mechanically robust tablet of low friability be produced.

In-vitro drug release, diametral crushing strength and tablet friability studies were performed on resulting tablets.

The tablets rapidly disintegrate *in vitro* releasing intact polymer-coated sustained-release pellets; the effect of compression force on drug release is shown. It is evident that slight damage to the film coat occurs as a consequence of pellet compression resulting in a slightly increased drug release rate. This increase in release rate however is marginal and the mechanism of dissolution appears not to be significantly affected.

Microphotographs of coated pellets prior to compaction and those released from the tablet following disintegration, show that some pellets appear to undergo physical deformation on compression.

Quantitative evaluation of the distribution of pellets within the compacted pellet tablet formulation was made by performing image analysis of sections of tablets composed of stained pellets. Quantitative evaluation of the pellet distribution within the diluent blend at the tablet surface, cross-sectional and side-view of the tablet is presented. Microphotographic evidence in support of the data relating to pellet distribution within the tablet matrix is also presented.

Investigations to determine the nature of the damage occurring to the film coat as a consequence of pellet compaction were carried out using scanning electron microscopy. Mehta and Jones (1986) discuss the importance of elucidating the integrity of polymeric films applied to dosage forms and how the technique of scanning electron microscopy provides a valuable tool facilitating qualitative evaluation of film coatings. Microphotography of tablet sections shows the effect of compaction on pellets at the tablet surface, cross-sectional and

side-views.

In order to quantify the extent of pellet damage it was necessary to consider the effect of compaction on *in-vitro* drug release. Comparison of drug release profiles of coated pellets presented as tablets with similar pellets studied as free entities indicates that drug release is more rapid after pellet compaction. The extent of physical damage caused to the film coat by compaction may be quantified by examining these differences in the *in vitro* release profiles. Square-root-time profiles indicate largely linear release for both free pellets and pellets presented as tablets. It is postulated that although pellet compaction may slightly enhance the rate of drug release by causing physical damage to the film coat of some pellets, it has little influence on the mechanism of drug release.

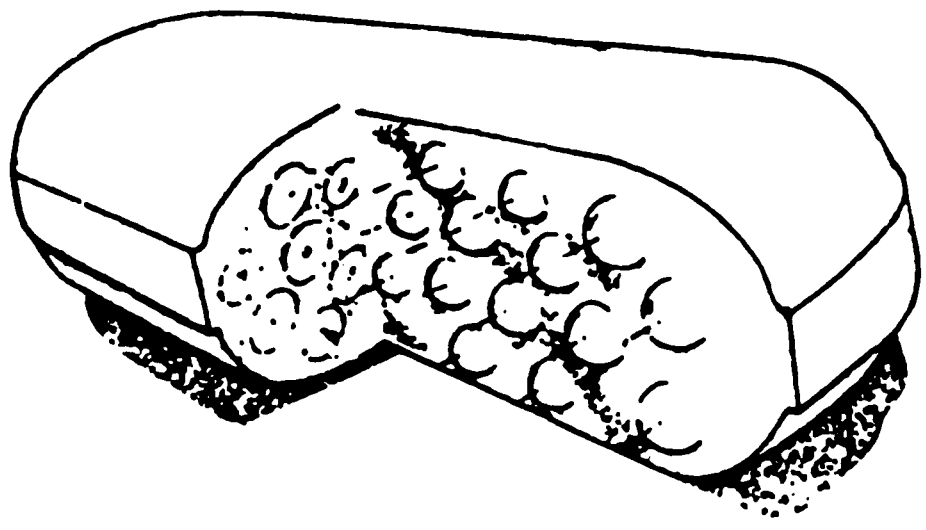


Figure 1.1. Schematic illustration of the compacted pellet concept.

CHAPTER 2

STUDY OF THE EFFECT OF FORMULATION AND PROCESSING VARIABLES ON THE PHYSICAL PROPERTIES OF UNCOATED PELLETS PREPARED BY EXTRUSION-SPHERONISATION

2.1. Introduction.

The physiological and pharmacological advantages associated with a sustained release multiple-unit delivery system for oral administration have been discussed previously. The technique of pelletization lends itself extremely favourably to the presentation of low potency drugs in the form of a multiparticulate preparation due to it being possible to prepare pellets containing high percentages of drug (as high as 90%w/w). Furthermore a drug delivery system comprising polymer-coated multiparticulates embedded within an inert rapidly disintegrating tablet matrix offers a means of presenting a low potency or high-dose drug as a sustained release multiple-unit preparation.

2.1.1. Pelletization by extrusion-spheronisation.

Spheronisation is a technique of Japanese origin which enables the formation of spherical particles with advantages of regularity of shape, uniformity of size and smooth surface characteristics. These particles have low friability associated with few fines. The use of this technique facilitates the formation of pellets containing very high percentages of drug; this is advantageous in the administration of high-dose or low potency drugs. Conine and Hadley (1970) reported that in many cases it is possible to prepare spheres containing 90-95 percent of active ingredient. The maximum drug content which may be achieved however is very much dependent upon the characteristics of the raw materials, in particular the binding and cohesive properties of the active ingredient(s).

For active excipients which are insoluble in the presence of the granulating fluid, spheres containing as much as 90 percent drug may be achieved.

The process of pellet formation leads to a densification of materials. This factor together with the high concentrations of drug

which may be achieved render spherical particles or pellets, an ideal preparation for presenting high dose drugs in the form of a solid oral sustained drug delivery device.

The processing stages in the technique of extrusion-spheronisation are summarised in Figure 2.1.

2.1.2. Detailed consideration of the pelletization process.

The pelletization process involves sieving and dry mixing of the excipients in a granulator. Granulating fluid is slowly added to the blend with mixing; mixing continues until a heavy, plastic, cohesive mass results. The quality of the wet mass at this stage is critical as it facilitates or otherwise, the formation of cylindrical segments or extrudate and spheres as a consequence of the extrusion and spheronisation processing. The granulate is inherently quite dense and is free-flowing.

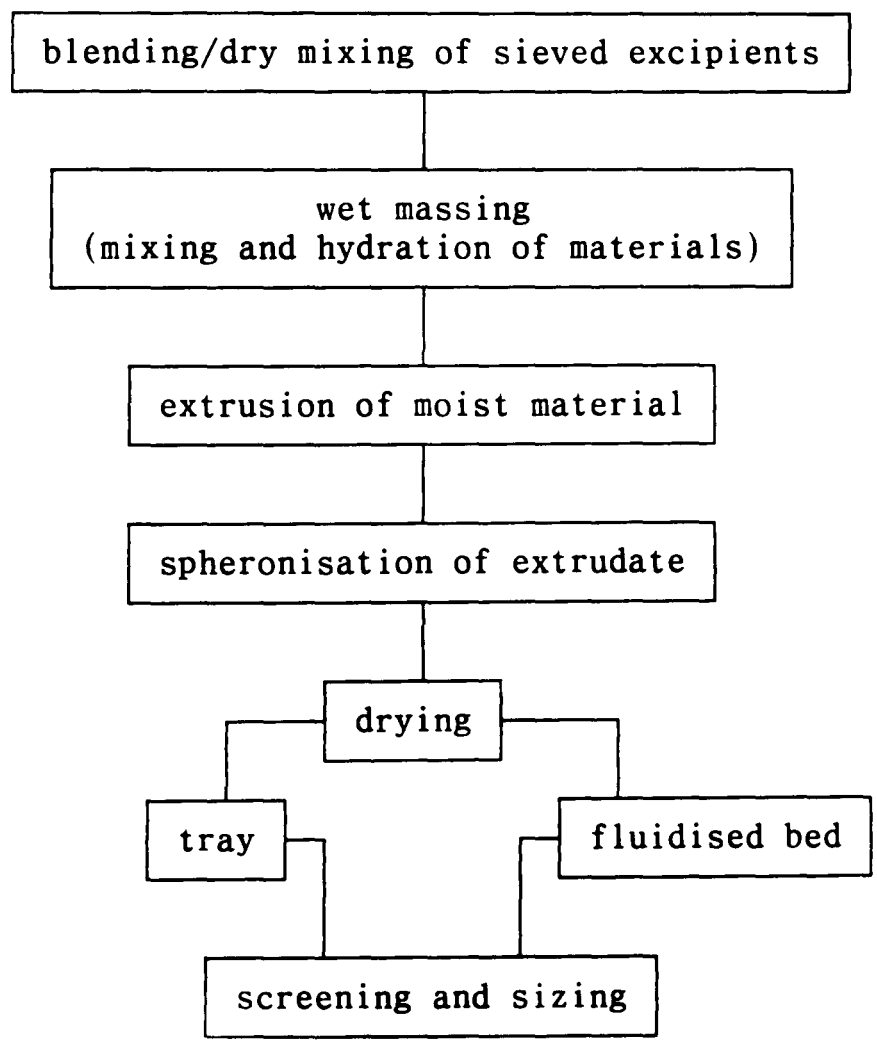


Figure 2.1. Summary of the stages involved in pelletization.

Granulated material is fed into the hopper of the extruder which consists of two contra-rotating cylinders, one of which is perforated and the other of which is solid. The material is forced through the holes of the perforated cylinder and the resultant product discharged as cylindrical segments or extrudate of uniform length. The length of the resultant extrudate is a function of the positioning of a cutting blade. The final sphere size approximates the diameter of the extrudate; it is however influenced by some processing variables including water content, spheroniser rotation speed and residence time.

Reynolds (1970) indicated the importance of the granulated material being thoroughly and uniformly wetted, such that a dense uniform mass results which will exhibit sufficient plasticity to enable it to be forced through the perforated cylinder of the extruder forming smooth, uniform quality extrudate.

Surface defects of extrudate in the form of roughness, cracks or circumferential ridges (termed "shark skinning") must not be evident as this leads to poorly controlled processing (Rowe, 1985). This is because initial breakage of the extrudate occurs randomly resulting in poorly shaped spheroids with a large particle size distribution. Excessive wetting at the granulation stage leads to serious problems in the spheronisation process, since particle agglomeration occurs thus impeding particle rounding.

Extrudate is then formed into spheres by means of a Spheroniser or Marumeriser. This involves breaking the cylindrical segments into shorter lengths by the action of a grooved plate spinning in a horizontal plane within a stationary vertical cylinder. Secondary to this, extrudate is transported by centrifugal force to the periphery of the spheroniser plate and is rounded by a rolling action generated by frictional forces and the rapid rotation of the roughened plate. The material is forced up the stationary wall of the spheroniser and as the

momentum is dissipated, it falls. This motion causes the material to form spheroids after a residence time upwards of a few minutes.

Some solvent evaporation occurs with densification of material during the spheronisation process; a densification "clink" is audible as this occurs, beyond which stage further spheronisation will not result in further rounding of the pellets. If the material is not sufficiently plastic to enable sphere formation by the action of the rotating plate, water will still be evaporated off as densification occurs, however the resultant pellets will be more oval than spherical.

The nature of the spheroniser plate and other factors, namely plate weight, rotation speed and residence time all influence the nature of the final product and must be carefully optimised. The final product must be of uniform spherical shape exhibiting smooth surface characteristics. An increase in the spheronisation speed and a prolongation of residence time will result in enhanced product density (Conine and Hadley 1970). As a generalisation however, the diameter of the spheres approximates the diameter of the extrudate.

The penultimate stage in pelletization involves the drying of the spheres. Conine and Hadley (1970) and Reynolds (1970) both state that the pellets may be dried by conventional methods, including air drying, oven or tray drying and fluidised bed drying and that fluidised bed drying will result in a product of greater bulk density than by the other methods. Many authors including Jalal et al. (1972) and Zhang et al. (1990) report the use of the hot air oven for drying spheres. This work illustrates that the drying method is of paramount importance in determining the physical properties of uncoated spheres, including variables such as diametral strength, elasticity, pore structure and skeletal density.

2.1.3. The significance of inert excipients in pelletization.

Pellet crushing strength, friability, size, shape and dissolution characteristics depend largely on the nature of the excipients used in pellet manufacture. The characteristics of the active ingredient is however of primary importance for pellets containing very high levels of drug.

It is widely accepted that microcrystalline cellulose is the excipient of choice as a filler, since it exhibits the elasticity and plasticity required for extrusion-spheronisation. It is a material which has the ability to take up water into its intraparticulate voidage and become readily deformable (Harrison et al. 1985).

The process of extrusion requires that the blend is of a cohesive nature exhibiting a degree of plasticity facilitating sphere formation. The mass must be free-flowing but of sufficient binding capacity to enable sphere formation; if the binding capacity of the drug and other excipients is not sufficient it may be necessary to add a binder. The literature frequently reports however that microcrystalline cellulose offers strong cohesive properties to the blend. Microcrystalline cellulose is used widely in the manufacture of spheres; as a wet mass it is readily deformable and its inclusion in the formulation will improve the extrusion process and extend the region of steady state flow (Harrison et al. 1985). It may be that the inclusion of a high proportion of microcrystalline cellulose in the product however will result in a higher incidence of surface defects to the extrudate. A reduction in the rate of extrusion may be all that is necessary to restore the quality of the extrudate (Harrison et al. 1985). Ghebre-Sellassie (1989) reports that the penetration of liquid into a pellet is proportional to the porosity or mean pore-diameter of the pellet and that the porosity of the pellet therefore influences the rate of disintegration. For a porous system, the pellet will disintegrate

more rapidly with the possible benefits of faster drug release.

The nature of the excipients used in pellet formulations contributes to the quality of the end product, including particle shape, smoothness, porosity, drug release characteristics and other physical parameters including diametral strength, elasticity and friability. The effect of the inert excipients on these parameters however becomes less important for pellet formulations containing high percentages of drug.

2.1.4. Granulating fluid volume.

The volume of water added to the blend at the granulation stage is critical. If the mass is too dry an excessive quantity of fines will result during the manufacturing process and in the end product. Conversely, too much granulating fluid will result in adherence of material to the equipment and particle agglomeration.

Malinowski and Smith (1975) investigated the effect of the initial water content of the mass on the physical properties of the end product. They report that an increase in water content leads to increases in the spheroid flow rate, bulk density and overall mean sphere diameter. They also report reduced product friability and the generation of fewer fines with increasing water content.

2.1.5. Processing variables and pellet quality.

a) Extrusion.

It is possible to modify the characteristics of the final product by adjusting the rate of extrusion of the granulated material. An increased extrusion rate will extend the region of steady state flow, with a corresponding improvement in the quality of the extrudate (Harrison et al. 1985). Excessive extrusion rates in excess of the critical velocity will lead however to surface defects or sharkskinning due to the generation of higher wall stresses during this process. In the interest

of final product uniformity therefore this critical velocity extrusion speed must not be exceeded.

As previously discussed, for the extrudate to break evenly during the spheronisation process, it must be smooth and of uniform diameter. For extrudate exhibiting sharkskinning, random breakage will occur and this will result in non-spherical, non-uniform pellets with a wide particle size distribution (Bechgaard and Nielsen 1978).

b) Spheronisation.

Spheronisation plate weight, residence time and rotation speed all influence the nature of spheronised particles. Conine and Hadley (1970) reported that the shape, diameter and particle size distribution are all influenced by the spheroniser rotation speed. There is an optimum speed below which there is no granule densification; only cylindrical granules will be produced due to an insufficient centrifugal force (Conine and Hadley, 1970 and Rowe, 1985). For a rotation speed in excess of the optimum, agglomeration of spheres will occur rapidly with the resultant material being oversize. Several authors report that for any given formulation an increase in the spheroniser rotation speed will lead to increased bulk density [Conine and Hadley (1970), Malinowski and Smith (1975) and Woodruff and Nuessle (1972)], an increased granule flow rate, a decreased mean particle size, a decreased friability and an increased percentage of fines (Malinowski and Smith, 1975).

The spheroniser residence time similarly affects the shape, diameter and particle size distribution of the spheroids. Assuming the minimum spheronisation rotation speed is exceeded then an increase in residence time will improve the sphericity of the pellets (Rowe, 1985). Increasing the residence time therefore leads to an increase in the granule flow rate (Malinowski and Smith, 1975), bulk density (Conine and Hadley, 1970 and Malinowski and Smith, 1975) and the pellet density (Rowe, 1985). There will also be a decrease in the friability of the particles and a

reduction in the percentage of fines produced.

c) Drying.

Chein and Nuessle (1985) showed that for materials within the core formulation which are soluble in the granulating fluid, the drying rate has a significant effect on the disintegration time of the pellets. An increased drying rate will lead to an increase in solute migration and a corresponding increase in the spheroid disintegration rate. It is an aim of this study to demonstrate the effect of the drying method and therefore the drying rate, on the physical properties of pellets prepared using the techniques of extrusion and spheronisation, including its influence on the diametral strength of pellets, porosity and skeletal density and the *in-vitro* drug release characteristics.

2.2. Materials and Methods.

2.2.1. Materials.

Ibuprofen (Boots Pharmaceuticals); Avicel PH101, RC591 and CL611 (FMC Corporation) and lactose NF Fast Flo (Wisconsin Dairies, Foremost Ingredient Group) were used in the pellet formulations documented subsequently. Purified water BP was used in all massing procedures.

2.2.2. Plant and Equipment.

Detailed in Table 2.1 is the equipment used in the manufacture of uncoated pellets. Two manufacturing locations were used throughout the study representing bench scale and pilot scale equipment. The physical properties of pellets manufactured using equipment which differed only in capacity, resulted in products which are in essence very similar. This is supported by data given hence. Bench scale formulations were studied at the academic establishment and pilot scale at the industrial establishment respectively. The batch sizes indicated represent the weight of dry solids.

LOCATION	
academic	industrial
Hobart granulator (capacity 1.5kg) Alexanderwerk GA65 Extruder Caleva Spheroniser (120mm diameter plate) Aeromatic AG Fluid Bed Dryer (1kg capacity)	Diosna P25 granulator (capacity 4kg) Alexanderwerk GA65 Extruder Caleva Model 15 Spheroniser Aeromatic AG Fluid Bed Dryer (10kg capacity)
0.59mm, 1.19mm and 1.41mm aperture sieves	
NB: Hot Air Oven (used only where indicated)	

Table 2.1. Equipment used in pelletization processing.

2.2.3. Blending of raw materials.

The solid excipients were weighed and passed into the granulator through a sieve of aperture 1.19mm, dry mixed for two minutes and the required volume of water added slowly to the blend (over 60 seconds) with the mixer on low setting. With the mixer on high setting the mass was blended for a period of time such that uniform distribution of the water resulted in granulated mass which was free-flowing but cohesive under compression.

During the granulating stage the mixer was stopped periodically and the mass redistributed thus eliminating any dead spots within the mixer and enabling redistribution of any material adhering to the wall of the mixer. The end point of the mixing process is very much dependent upon the nature of the mass of a given blend. This is not only dominated by the nature and quantity of the excipients forming the mass but also by the quality of the mixing process.

2.2.4. Extrusion of granulate.

The success of the extrusion process and the nature of the extrudate is largely a function of the nature of the formulation and extrusion process itself. Granulate must be free-flowing, but cohesive and plastic enough to allow it to be forced through the perforated cylinder of the extruder. The extrudate must be of uniform diameter and length, with smooth surface characteristics and free-flowing.

The rate of extrusion is critical. For smooth surface, uniform extrudate to be produced the rate of extrusion must be carefully controlled. The Alexanderwerk GA65 Extruder was operated with a perforated cylinder rotation speed of 98 rpm.

2.2.5. Spheronisation.

For each formulation the spheronisation rotation speed and residence time were carefully optimised in a preliminary feasibility study. Differences in the scale of the spheronisation equipment available and the spheronisation plate weights were therefore compensated for by adjustment of the rotation speed and residence times. Specific information relating to spheronisation plate weights, residence times and rotation speeds are given subsequently in Tables 2.2 to 2.5 inclusive.

2.2.6. Drying.

Pellets were dried using either fluidised bed apparatus with an inlet temperature of 58 to 60°C, or by tray drying in a hot air oven using a drying temperature of 45 to 50°C. Pellets containing either ibuprofen or lactose with microcrystalline cellulose were prepared in order that the effect of aqueous solubility of the main excipient on pellet physical properties could be evaluated, as a consequence of these two very different drying techniques. A fundamental difference in the two processes is the length of the drying process. It is postulated that

the lactose-containing pellets, in which the main excipient is freely water-soluble, may be more susceptible to solute migration as a consequence of the slow water removal associated with tray drying, than the ibuprofen-containing entities.

Quantitative consideration of the effect of the drying methodology on the physical and release properties of pellets is documented in section 2.3.

2.2.7. Moisture content.

All batches of spheronised material were dried thoroughly to a moisture content of not greater than 1%w/w.

2.2.8. Sizing.

Removal of agglomerates and fines was performed for each batch by gently passing dried material through a sieve of aperture 1.41mm and over a sieve of aperture 0.59mm prior to any quantitative evaluation of pellets.

2.2.9. Determination of skeletal density and sample specific volume.

A Multivolume Helium Pycnometer 1305 was used to determine the skeletal density and volume of uncoated pellets, which enabled calculation of the absolute density based on the weight of the sample.

Use of the Micromeritics Multivolume Pycnometer 1305 enabled measurement of the skeletal volumes of pellets by observing the reduction in the gas capacity in the sample chamber as a direct consequence of the presence of the sample. Helium penetrates the smallest pores and surface irregularities and therefore the volume obtained enabled calculation of the ultimate theoretical density of the sample.

The sample chamber loaded with the test sample was charged to a gas pressure of approximately 20 psig (P_1); 1 psig is equivalent to

6.895 x 10^{-3} MPa. This volume of gas was then allowed to expand into a second chamber (of known volume), previously at the same temperature and pressure; this results in a second pressure (P_2). This pressure becomes progressively smaller as the sample size increases. The use of the mass balance equations for the gas enabled calculation of the sample volume, since the volumes of the empty sample chamber and the expansion chamber and the pressure drop ratio upon expansion, were known.

It was necessary to ensure that the sample chamber and sample cup were free from particulate contamination before any measurements were made; the pycnometer was therefore cleaned thoroughly prior to use. For each formulation, the sample cup (of nominal volume less than 5cm^3) was filled with pellets; the sample chamber was purged with Helium gas prior to reading to ensure the displacement of any residual air or moisture which may have been present within the pore structure of the sample.

The sample chamber was then charged to a Helium gas pressure (P_1) of approximately 19.5 $\pm$ 0.2 psig (equivalent to approximately 0.134 MPa), allowed to equilibrate and the pressure recorded. By opening the valve connecting the sample and expansion chambers, the Helium was then allowed to expand into the expansion chamber, equilibrate and the expansion pressure (P_2) was recorded. The chamber was then vented and the pressure allowed to return to zero. This procedure was repeated 10 times for each sample and a mean value obtained. The weight of the sample and the empty sample cup were recorded at the end of testing; this ensured that the weight recorded reflected the true weight of the sample free of air and moisture vapour.

Prior to use the instrument was calibrated by determining the sample volume of a precision ball bearing, which by design occupied the maximum possible volume of the sample cup.

2.3. Results and Discussion.

2.3.1. Uncoated pellet formulation for a low potency drug.

Tables 2.2 and 2.3 show the processing variables for pellet formulations containing high percentages of ibuprofen with Avicel PH101. For any dosage form containing inherently high percentages of the active ingredient, the characteristics of the drug will significantly influence the success of the manufacturing process and consequently the physical characteristics of the end product. The physical properties of the drug, the nature of other excipient(s) and their relative quantities are all factors which affect the success of the pelletization process. Avicel PH101 is documented as enhancing the spheronisation process (Ghebre-Sellassie, 1989) not only for its use as an inert filler, but also for its binding capacity. Microcrystalline cellulose as a spheronisation enhancer imparts the binding properties necessary for pellet strength and integrity and also confers that plasticity necessary for extrudate and sphere formation.

The extrusion and spheronisation technique was successfully applied here to pellet formulations containing up to 80%w/w ibuprofen with Avicel PH101. Increasing the drug content beyond 85% was however largely unsuccessful. The binding capacity of microcrystalline cellulose appeared to be exceeded for pellet formulations containing drug concentrations in excess of 80 to 85%w/w. If drug levels in excess of this were to be achieved it would be necessary to use an additional binder within the pellet formulation. Some pellets were therefore prepared containing RC591 and CL611 grades of Avicel. These grades of microcrystalline cellulose contain incorporated sodium carboxymethyl cellulose (NaCMC). It was elucidated by preparing pellets containing NaCMC-grades of Avicel that the price of increasing the drug loading beyond 85%w/w was impaired pellet quality. In addition, Ghebre-Sellassie (1989) reported that pellet systems containing NaCMC grades of

microcrystalline cellulose exhibited differing drug release mechanisms: NaCMC-containing pellets exhibit release properties characteristic of hydrogel matrices as opposed to those containing only microcrystalline cellulose, which behave as inert matrices. A consequence therefore of the increased binding capacity associated with the use of NaCMC is poor sphericity in addition to an influence on the drug release mechanism. The reported change in geometry of NaCMC-containing pellets behaving as water swellable hydrogel matrices when in contact with the aqueous dissolution medium (Ghebre-Sellassie, 1989) was considered to be an undesirable consequence associated with the use of these excipients, in return for a slightly increased drug loading (in excess of 80% ibuprofen). The processing conditions for those pellet formulations containing ibuprofen with Avicel PH101 therefore were optimised; details are given in Tables 2.2 and 2.3.

The effect of the scale of manufacture on the resultant product was studied within the scope of this work. Pellets were prepared using laboratory and pilot scale equipment differing in the granulation and spheronisation stages (Table 2.1). Figure 2.2 illustrates the difference in the *in-vitro* release profiles for uncoated pellets containing 80%w/w ibuprofen prepared using laboratory and pilot scale equipment. It is apparent that the processing scale has little effect on the *in-vitro* release properties from such pellets.

During processing it became evident that critical processing variables including the volume of the granulating fluid, the length and severity of the wet massing process, the rate of extrusion and the rate and extent of spheronisation, all had a significant effect on the quality of the resultant product. The manufacturing process was therefore carefully optimised for each pellet formulation.

processing scale	pilot	pilot	pilot
batch size (solids) kg	4.0	4.0	4.0
<u>ingredients</u> (%w/w)			
ibuprofen	80	70	60
Avicel PH101	20	30	40
Purified water BP	52.5	57.5	62.5
<u>spheronisation details</u>			
plate weight (kg)	5.543	5.818	5.656
rotation speed (rpm)	552	600	649
residence time (mins)	8	8	9
drying method	fluidised	fluidised	fluidised
drying time (mins)	90	90	90
moisture content (%w/w)	0.6	0.5	0.3

Table 2.2. Effect of drug loading on the processing variables for uncoated pellets containing ibuprofen (pilot scale).

processing scale	laboratory	
batch size (solids) kg	1.5	
<u>ingredients</u> (%w/w)		
ibuprofen	80	
Avicel PH101	20	
Purified water BP	56	
<u>spheronisation details</u>		
plate weight (g)	75	
rotation speed (rpm)	1438	
residence time (mins)	4	
drying method	fluidised	tray
drying time (mins)	120	1440
moisture content (%w/w)	0.36	0.30

Table 2.3. Processing variables for fluidised bed and tray dried pellets containing 80%w/w ibuprofen (laboratory scale).

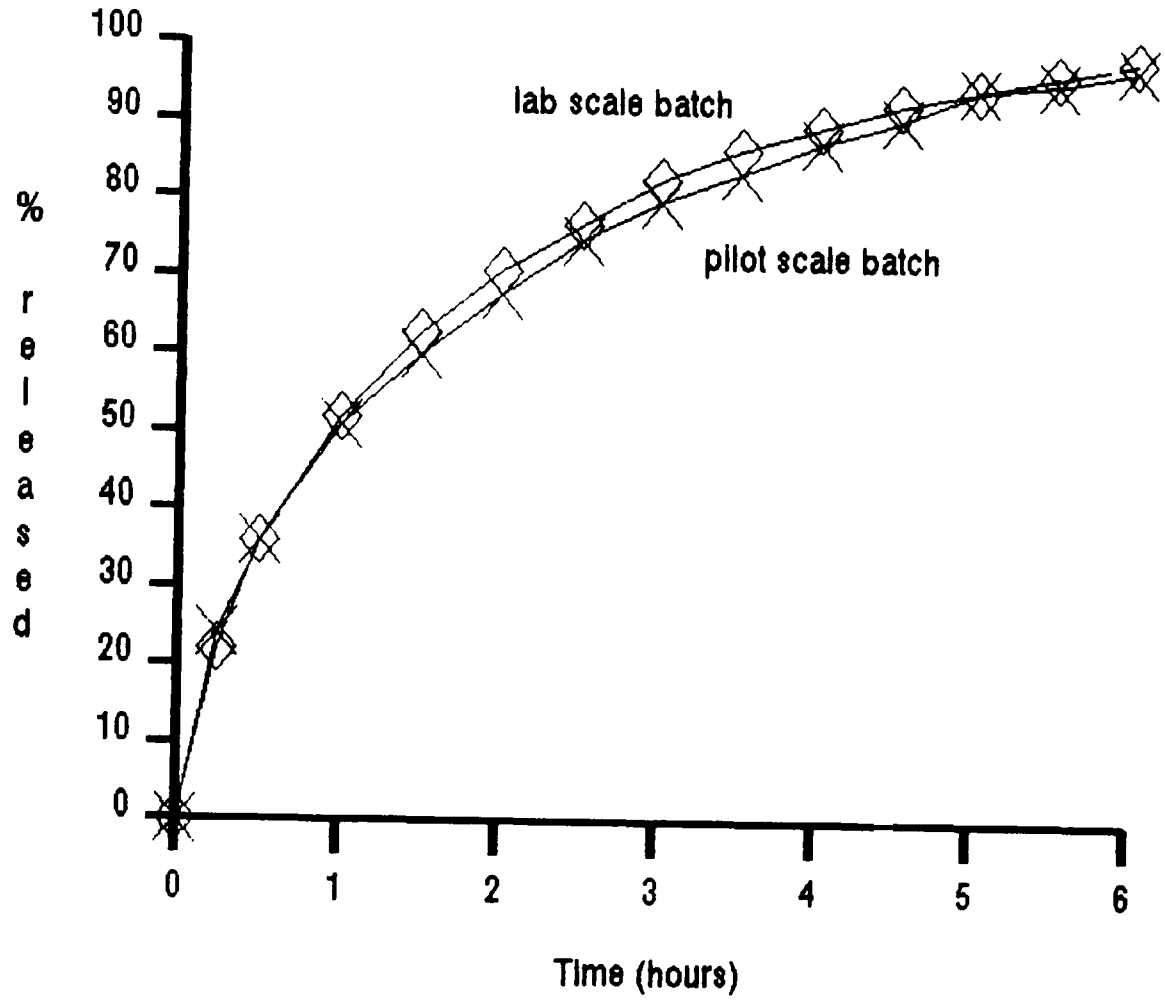


Figure 2.2. Effect of processing scale on *in-vitro* drug release from uncoated pellets containing 80%w/w ibuprofen.

It became apparent that insufficient wetting of the granular material results in excessive fines generation and that an excess of oversize material may be attributable to too high a water content or binder concentration, or too high a spheronisation rotation speed. Optimisation of the moisture content at the wet massing stage yields spheres of particle size approximating the diameter of the extrudate.

processing scale	pilot		pilot	pilot
batch size (solids) kg	4.0		4.0	4.0
ingredients (%w/w)				
lactose NF Fast Flo	80		-	70
Avicel PH101	20		100	30
Purified water BP	37.5		112	45
spheronisation details				
plate weight (kg)	4.908		6.014	5.006
rotation speed (rpm)	603		502	602
residence time (mins)	7		6	6
drying method	fluidised	tray	fluidised	
drying time (mins)	60	1440	90	60
moisture content (%w/w)	0.63	0.6	no product	0.96

Table 2.4. Formulation and processing variables for placebo pellets (pilot scale).

processing scale	pilot	pilot	pilot
batch size (solids) kg	4.0	4.0	4.0
ingredients (%w/w)			
lactose NF Fast Flo	90	50	50
Avicel PH101	10	50	50
Purified water BP	27.5	60	50
Isopropyl alcohol	-	-	10
spheronisation details			
plate weight (kg)	4.373	5.708	5.357
rotation speed (rpm)	502	653	499
residence time (mins)	5	6	5
drying method	fluidised	fluidised	fluidised
drying time (mins)	45	90	90
moisture content (%w/w)	0.5	0.6	0.8

Table 2.5. Formulation and processing variables for placebo pellets (pilot scale).

2.3.2. Placebo pellet formulation.

Placebo pellets formulations were studied for reasons which are discussed in Chapter 7. Optimised pellet formulations containing lactose and microcrystalline cellulose were therefore prepared at least in part, to ascertain the effect of the drying technique on the physical properties of pellets (section 2.3.5) as a function of the aqueous solubility of the pellet components. Tables 2.4 and 2.5 summarise the processing variables for those placebo pellets prepared.

The effect of formulation variables on the diametral strength of both placebo and active pellets is discussed in Chapter 6.

2.3.3. Particle size distribution.

The particle size distribution of pellets directly affects the overall surface area. The particle size distribution must be as narrow as possible to ensure minimum variation in the coating thickness within the batch of pellets. Also for the compression of pellets into tablets, it is anticipated that segregation may be minimised by a narrow particle size distribution.

Conine and Hadley (1970) reported that the mean particle size of pellets prepared by extrusion and spheronisation approximates the diameter of the extrudate. The GA65 Alexanderwerk Extruder used in this work was fitted with a perforated cylinder of screen size 1mm. Figure 2.3 shows a typical particle size distribution for an optimised pellet formulation prepared using the technique of extrusion-spheronisation; some 85 per cent of the product has a particle size of between 1.0mm and 1.25mm; there is little evidence of oversize or undersize material. It is apparent that the success of the pelletization process may be assessed to some extent by the quality of the particle size distribution of the dried product.

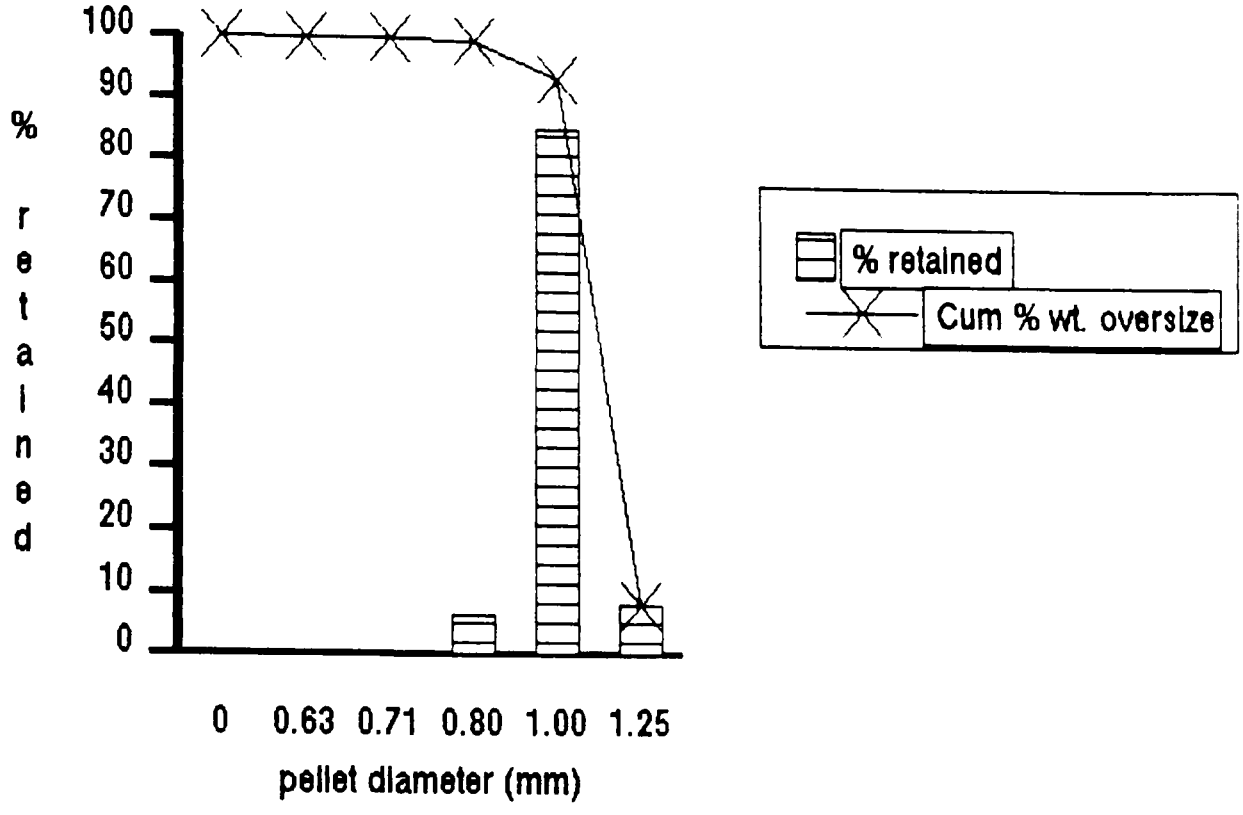


Figure 2.3. Particle size analysis of ibuprofen pellets containing 80%w/w drug (pilot scale).

In summary, optimisation of the processing variables of a pelletization process yields a product in which the mean particle size approximates the screen size of the perforated cylinder of the extruder. Particle size analysis was performed for all pellet formulations.

2.3.4. Calculation of the skeletal density and the sample specific volume of uncoated pellets.

The principle of operation of the Multivolume Pycnometer is described in Appendix 1.

The working equation for computation of sample volume is

$$V_{samp} = V_{cell} - \frac{V_{exp}}{(P_1/P_2 - 1)} \qquad \text{Equation 2.12}$$

where V_{samp} = sample volume

V_{cell} = empty volume of the sample cell with the empty sample cap in place

V_{exp} = expansion volume

P_1 = charge pressure (psig)

and P_2 = expansion pressure (psig).

Calculation of the V_{samp} value was performed using a computer program provided with the apparatus; the results were however also checked by calculation to ensure accuracy.

The density of a material is defined as weight per unit volume and may be expressed as follows:

$$\sigma_{samp} = \frac{W_{samp}}{V_{samp}} = \frac{\text{gross weight - cup weight}}{V_{samp}} \qquad \text{Equation 2.13}$$

where σ_{samp} = sample density

W_{samp} = sample weight

and V_{samp} = sample volume.

Sample specific volume (U_{samp}) is defined as the volume per unit weight and is calculated as follows:

$$U_{samp} = \frac{V_{samp}}{W_{samp}} = 1/\sigma_{samp} \qquad \text{Equation 2.14}$$

In summary, operation of the pycnometer depends upon charging the sample chamber to an elevated gas pressure (P_1), followed by expanding the pressure into a precisely known expansion volume (V_{exp}). Measurement of the final pressure (P_2) enables calculation of the sample volume. The larger the sample volume the lower the final pressure P_2, since larger

samples will reduce by displacement the amount of gas in the initial charge.

Figure 2.5 is a schematic illustration of the Micromeritics Pycnometer 1305:

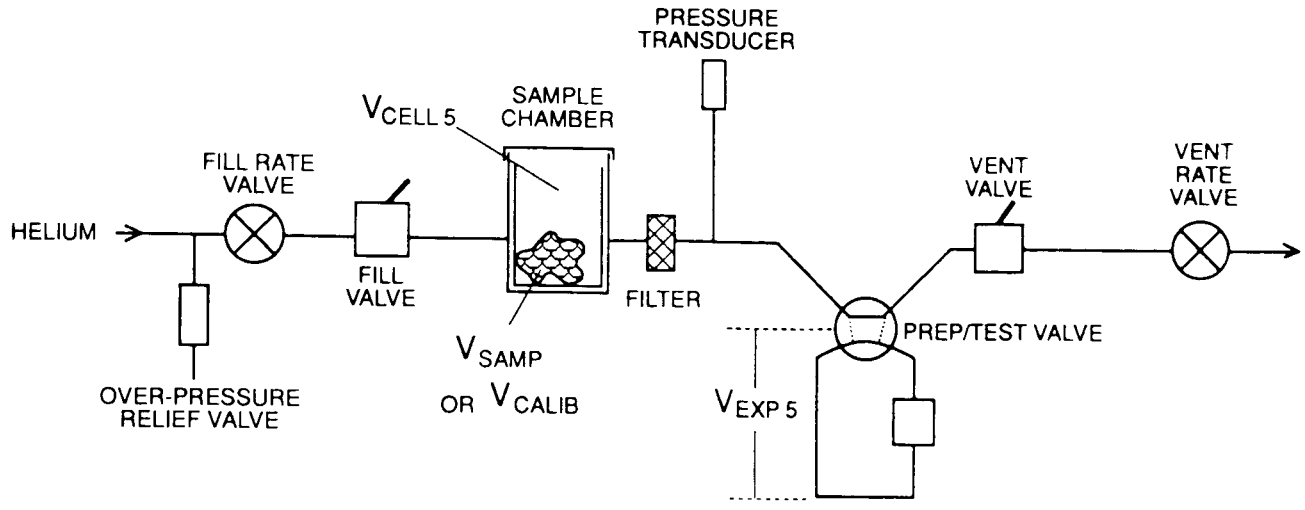


Figure 2.5. Schematic diagram of the Micromeritics Multivolume Pycnometer 1305.

2.3.4.1. Instrument calibration.

Calibration values were determined by measuring the P_1 and P_2 pressures using the $5cm^3$ sample chamber both with an empty sample cup and with the precision steel ball of known volume supplied with the instrument. Table 2.6 shows the quantitatively determined V_{cell} and V_{exp} values using previously described methods.

V_{cell}	$8.533cm^3$
V_{exp}	$6.307cm^3$

Table 2.6. Computed calibration values for V_{cell} and V_{exp}.

2.3.4.2. Sample calculation.

Consider the following. A sample of uncoated fluidised bed dried ibuprofen pellets containing 80%w/w drug were placed in the $5cm^3$ sample cup, purged with helium gas and charged to a pressure (P_1) of 19.412 psig (0.134 MPa). The helium was then allowed to expand into the second chamber and the pressure drop upon expansion enabled the determination of P_2 = 10.405psig (0.072 MPa). Using the calibration data for V_{cell} and V_{exp}, the sample volume was computed using Equation 2.12, $V_{samp}=1.219cm^3$; this procedure was performed ten fold for each sample. The net sample weight was 1.447g. Table 2.7 shows the computed data for this sample.

The specific sample volume (U_{samp}) was calculated using Equation 2.14:

$$U_{samp} = \frac{V_{samp}}{W_{samp}} = 1/\sigma_{samp} \qquad \text{Equation 2.14}$$

Therefore, in this example, $U_{samp} = 1/1.188 = 0.842\ cm^3\ g^{-1}$.

The skeletal properties of all pellet formulations studied were assessed similarly and the results are expressed graphically in the following figures.

Figures 2.7 and 2.8 show the effect of drug loading on the skeletal properties of uncoated pellets containing ibuprofen and Avicel PH101. It is apparent that with increasing microcrystalline cellulose concentration there is a corresponding increase in pellet skeletal density. This is not unexpected on account of the nature of the inert component.

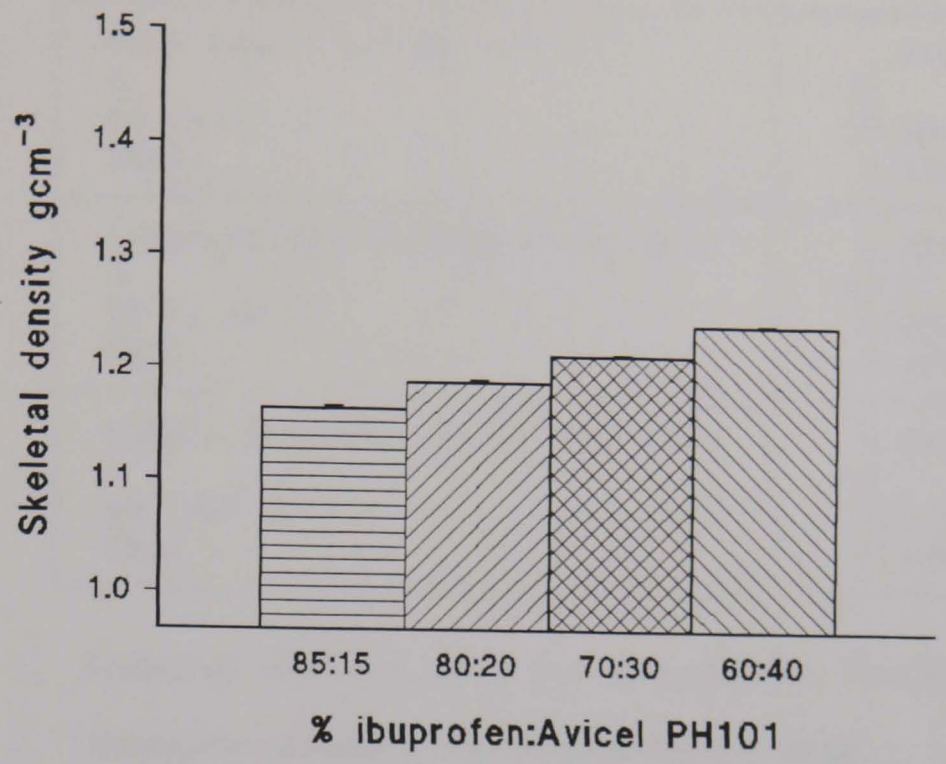


Figure 2.7. Effect of drug loading on the skeletal density of uncoated pellets containing ibuprofen and Avicel PH101.

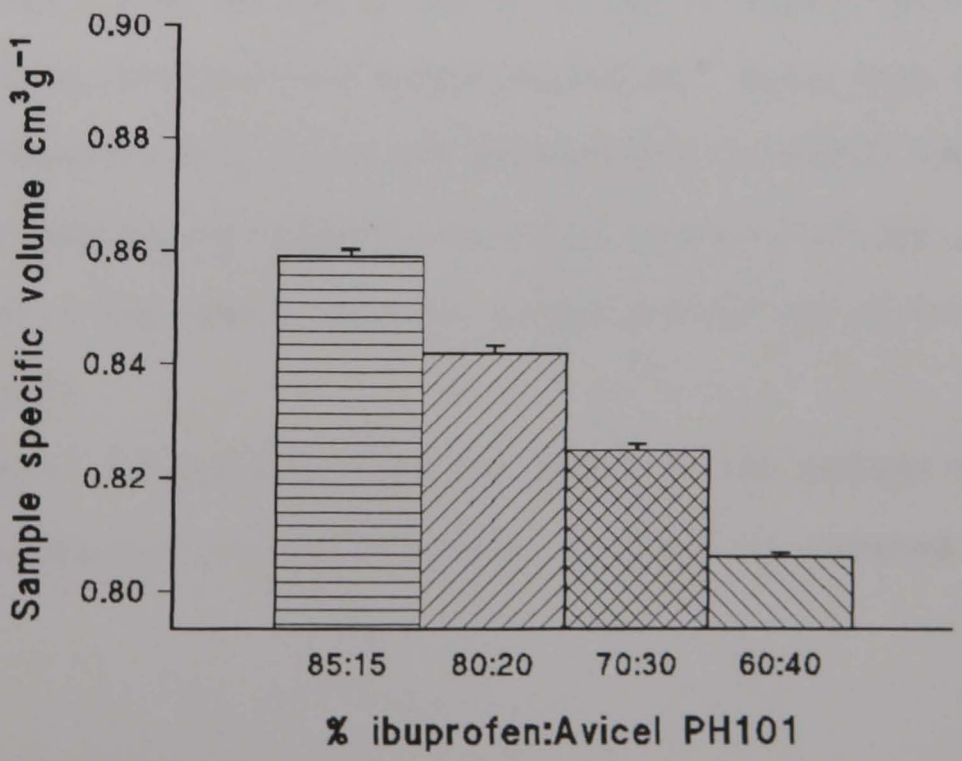


Figure 2.8. Effect of drug loading on the sample specific volume of uncoated pellets containing ibuprofen and Avicel PH101.

parameter	value
mean sample volume (cm^3)	1.218
n	10
SD (cm^3)	0.00213
%RSD	0.175
computed sample density (g cm^{-3})	1.188
n	10
SD (g cm^{-3})	0.00213
%RSD	0.179
sample specific volume (cm^3 g^{-1})	0.842
n	10
SD (cm^3 g^{-1})	0.00134
%RSD	0.159

Table 2.7. Computed skeletal data for a sample of fluidised bed dried ibuprofen pellets containing 80%w/w drug.

Microcrystalline cellulose contributes to the bonding mechanism and is largely responsible for the maintenance of pellet integrity due to its adhesive properties.

Pellets are largely held together by the formation of solid bridges formed with binder hardening and to a limited extent with a poorly water soluble drug, crystallised solute molecules. Hence with increasing binder concentration, it is not unreasonable to expect increasing particle density and diametral strength (Figure 6.6) and a corresponding reduction in the sample specific volume and the particle elasticity (Figure 6.7).

Figures 2.9 and 2.10 show the effect of the aqueous solubility of the main component on the skeletal properties of uncoated pellets.

Where the main excipient is freely water soluble (lactose), the degree of crystalline bond formation due to the presence of solute molecules during the pelletization process is much greater than where the main component exhibits poor aqueous solubility and therefore little tendency towards crystalline bond formation (ibuprofen). The mechanism of solid bridge formation is responsible for the fundamental bonding forces determining the strength of the formulation. These figures demonstrate admirably the effect of aqueous solubility on the resultant particle density. An excipient which is freely soluble in the granulating fluid exhibits greater particle density and mechanical strength than a pellet containing a poorly soluble component.

In spite of differences associated with laboratory and pilot scale pelletization processes, there appears to be little effect of the scale of processing on the skeletal properties of the resultant product (Figures 2.11 and 2.12).

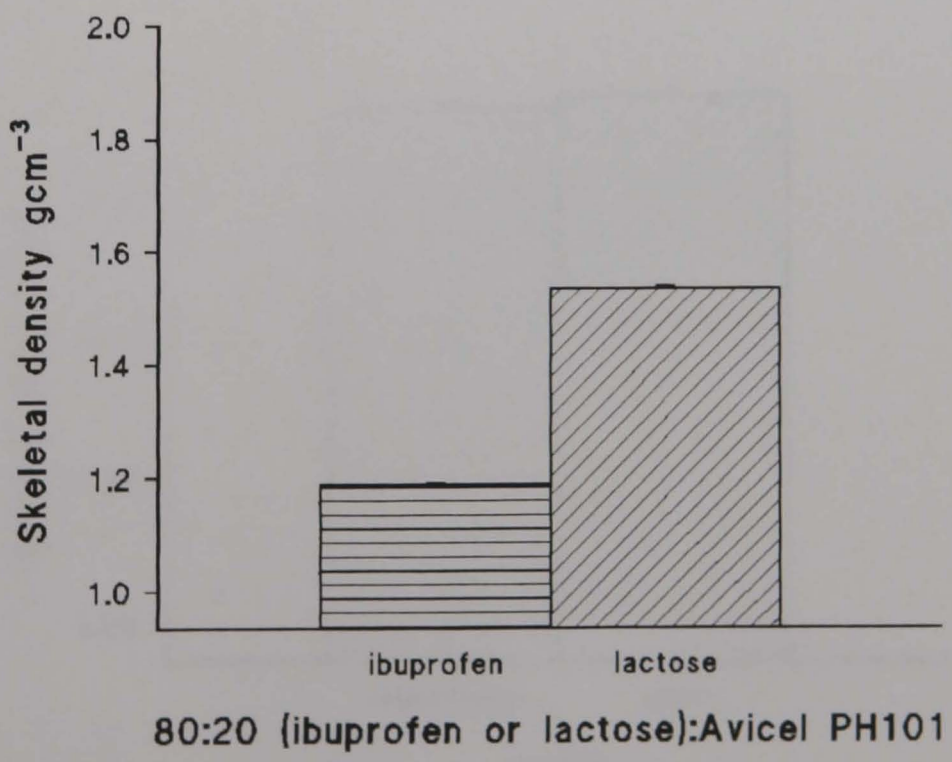


Figure 2.9. Effect of excipient aqueous solubility on the skeletal density of uncoated pellets.

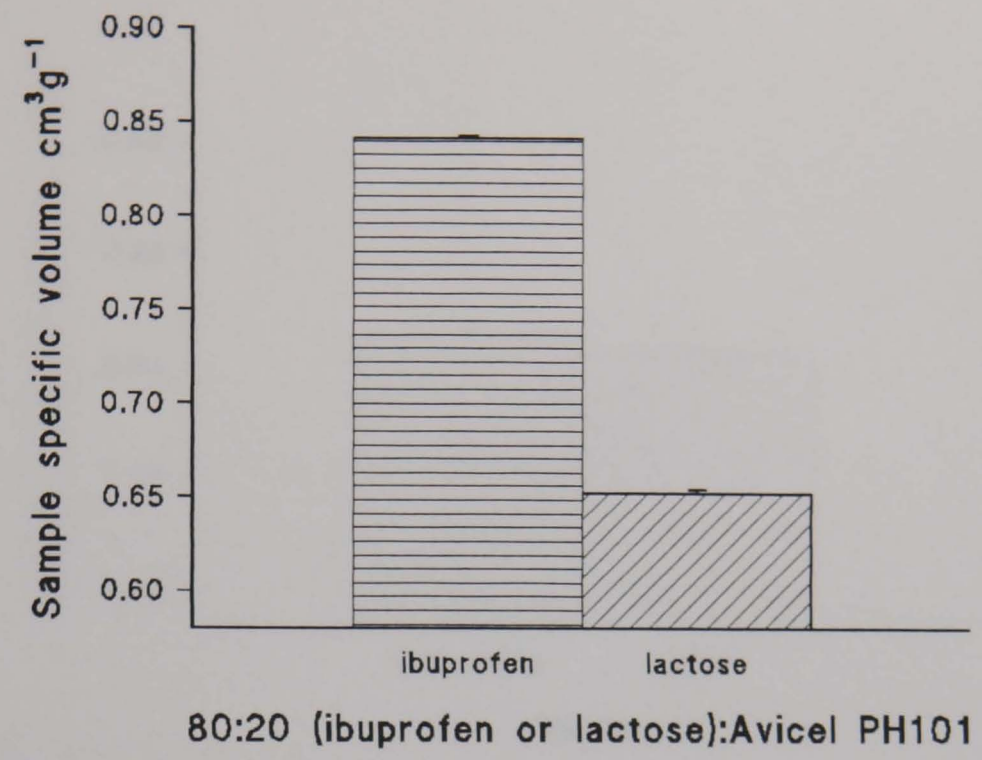


Figure 2.10. Effect of excipient aqueous solubility on the sample specific volume of uncoated pellets.

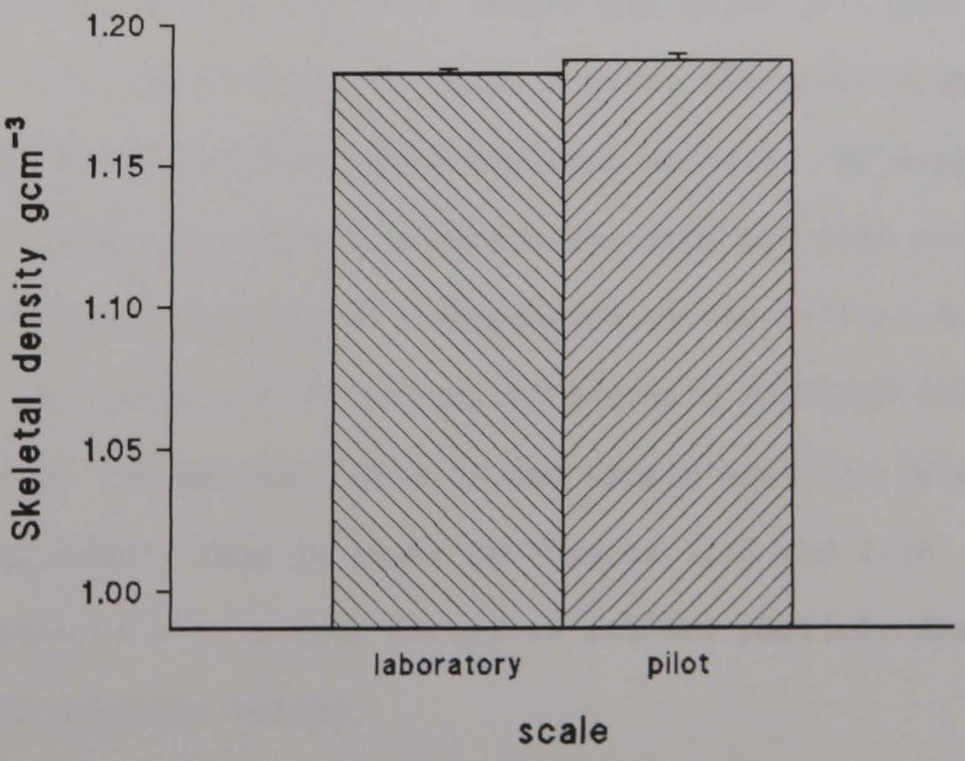


Figure 2.11. Effect of processing scale on the skeletal density of uncoated pellets containing 80%w/w ibuprofen.

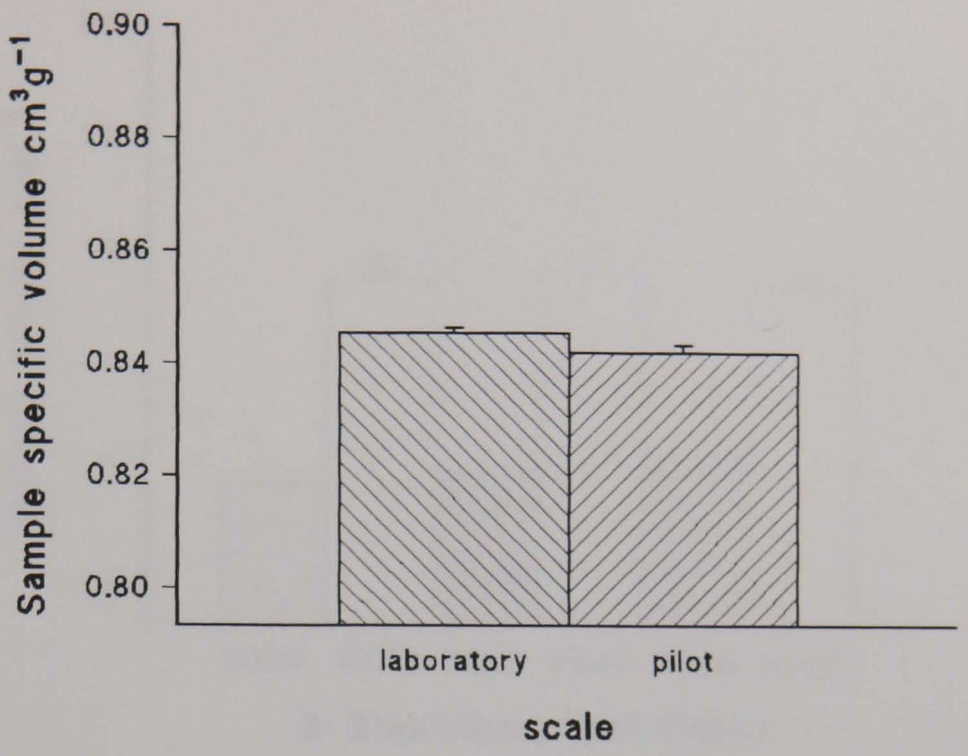


Figure 2.12. Effect of processing scale on the sample specific volume of uncoated pellets containing 80%w/w ibuprofen.

Figures 2.13 and 2.14 show the skeletal properties of drug-laden and drug-depleted uncoated pellets; before and after *in-vitro* dissolution testing. The shaded areas in these figures represent drug-laden and the non-shaded areas represent drug-depleted pellets. As might reasonably be expected, those particles from which the drug has been removed display similar skeletal properties irrespective of the initial drug loading.

The effect of a film coating of Eudragit RS/RL30D (12% solids increase) on the skeletal density and sample specific volume of pellets containing 80%w/w drug is shown in Figures 2.15 and 2.16. As expected the presence of a film coat serves to enhance particle density and reduce the sample specific volume.

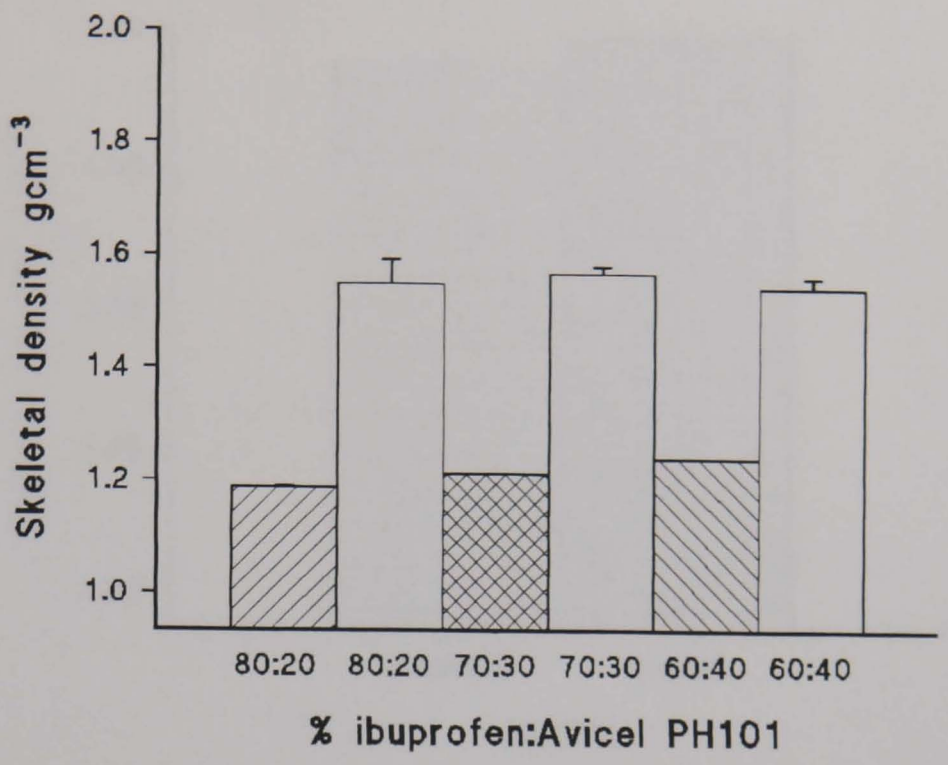


Figure 2.13. Comparative skeletal densities of drug-laden (shaded) and drug-depleted (non-shaded) pellets (uncoated).

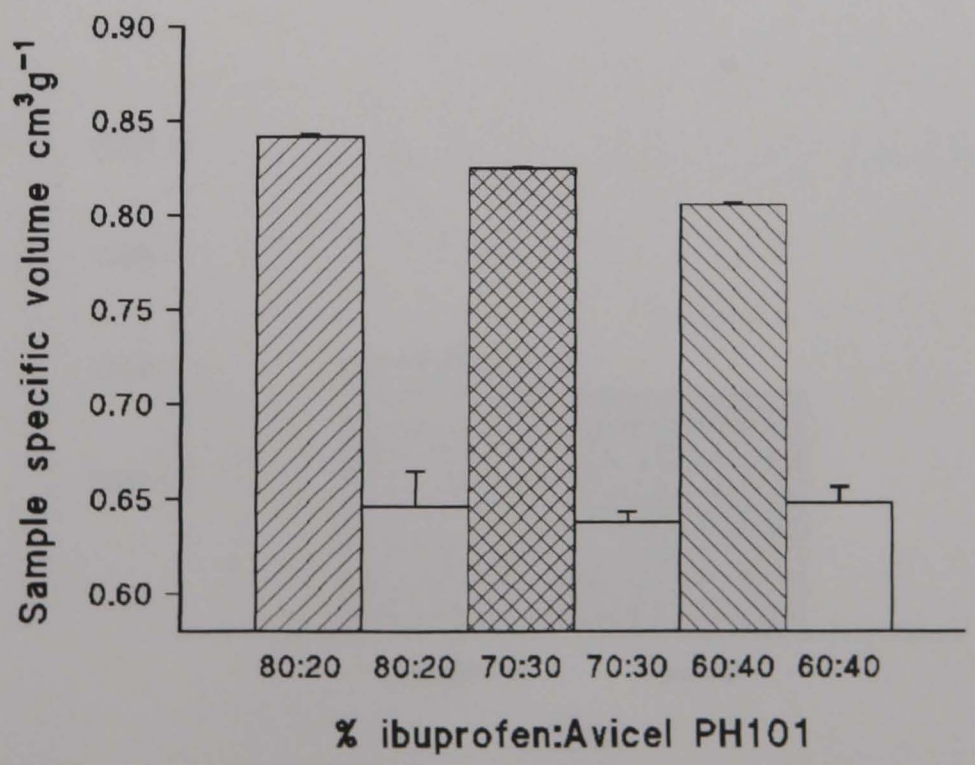


Figure 2.14. Comparative sample specific volumes for drug-laden (shaded) and drug-depleted (non-shaded) pellets (uncoated).

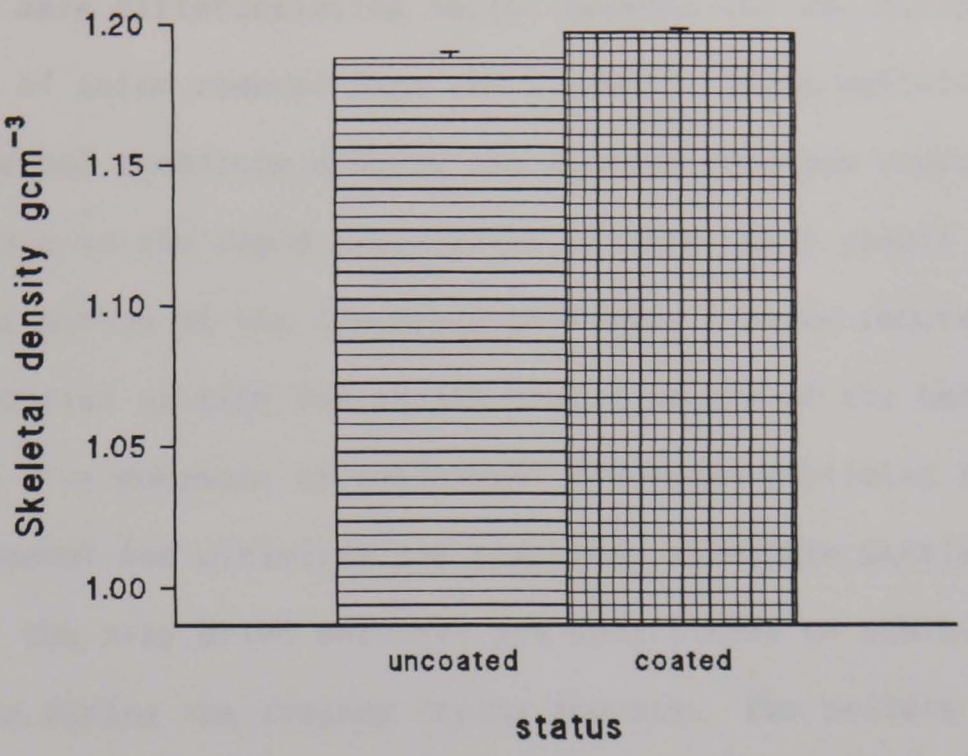


Figure 2.15. Effect of film coating (Eudgragit 12%w/w) on the skeletal density of pellets containing 80%w/w drug.

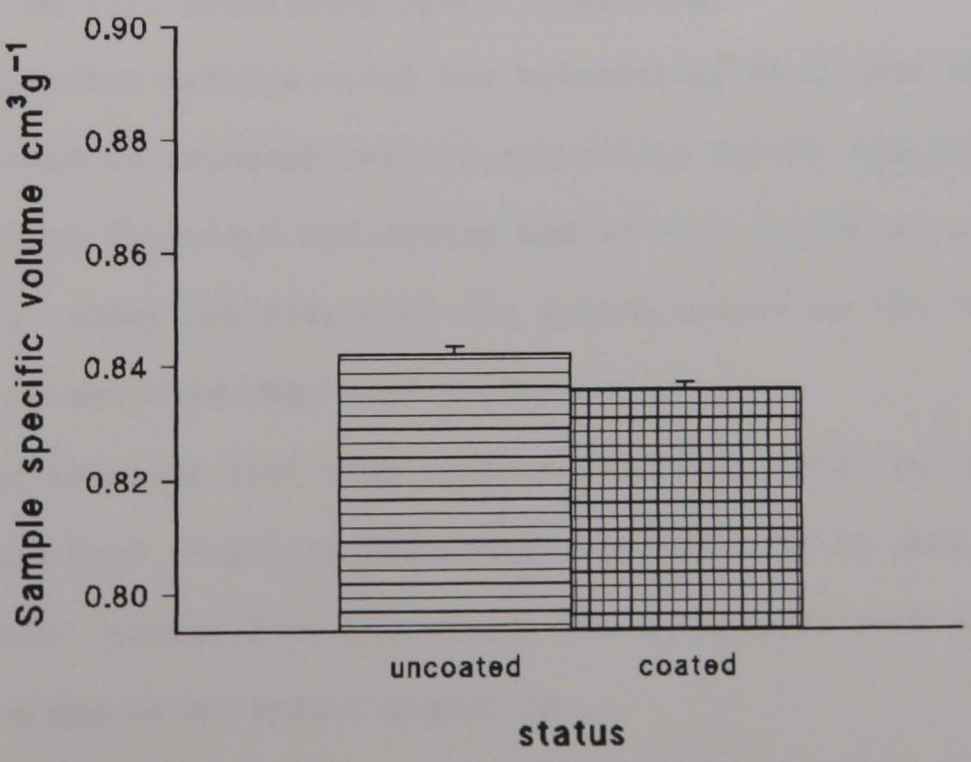


Figure 2.16. Effect of film coating (Eudgragit 12%w/w) on sample specific volume for pellets containing 80%w/w drug.

2.3.5. Consequence of drying method on the physical and release properties of pellets containing ibuprofen and lactose.

The main differentiating factor between the two drying methods is the rate of water removal from the product. Those pellets dried by fluidised bed technique achieve the desired moisture content much more quickly due to the rapid evaporation of water as a result of the turbulent motion of the fluidised particles. Water removal from tray-dried material is slow due to the static nature of the bed.

The free movement of individual fluidised particles leads to rapid water removal and minimises the migration of solute particles within the spheres; the tray dried entities are more likely to exhibit solute migration during the lengthy drying process. For pellets in which the main excipient lactose, which is freely soluble in the granulating fluid, solute migration is inevitable and is exacerbated by the slow drying associated with static bed dryers.

2.3.5.1. Effect of drying method on *in-vitro* drug release from uncoated pellets containing 80%w/w ibuprofen.

Dissolution testing using the methodology described in Chapter 4, was performed on uncoated pellets containing 80%w/w ibuprofen which had been dried by fluidised bed drying and by tray drying in a hot air oven. Figure 2.17 shows the effect of the drying method on the *in-vitro* release profiles of uncoated ibuprofen pellets.

It is apparent that drug release from tray dried pellets is slightly faster than from fluidised bed dried material. It is postulated that the slower water removal from the static bed associated with tray drying leads to a degree of solute migration.

It would appear that drug in solution migrates to the pellet surface as the water is slowly driven off during the lengthy drying period of 24 hours which is necessary with static bed drying.

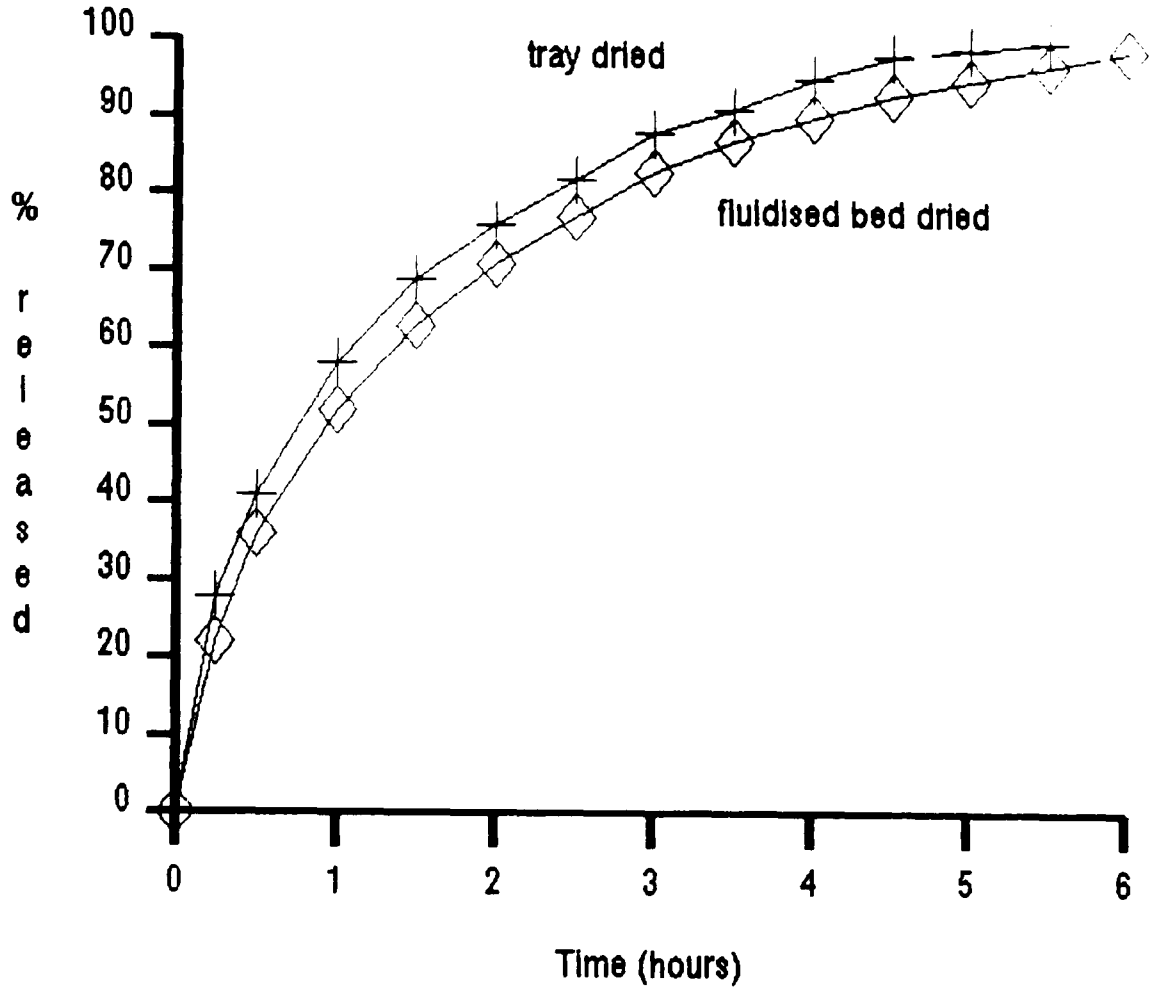


Figure 2.17. Effect of drying method on the *in-vitro* drug release from uncoated pellets containing 80%w/w ibuprofen.

Fluidised material however dries much more quickly and therefore this technique enables the use of a slightly higher drying temperature; the possibility of causing thermal damage to the product is reduced due to the continuous motion of fluidised particles. This factor together with rapid water removal enables a slightly higher drying temperature to be used for drying fluidised particles. Ibuprofen exhibits poor aqueous solubility and although one might expect little solvation of drug within the uncoated cores during pelletization, there is evidence of some dissolution of drug and solute migration. This phenomena is apparently minimised by the rapid drying of fluidised product (Figure 2.17).

2.3.5.2. Effect of drying method on pellet surface characteristics.

The pore structure of pellets can affect the capillary action of the dissolved drug and consequently influence the rate of release of drugs from pellets (Ghebre-Sellassie, 1989). The pore structure and the pellet surface characteristics also affect film deposition and formation. Figures 2.18 and 2.19 show scanning electron micrographs (SEMs) of the surfaces of the same batch of uncoated ibuprofen pellets dried using fluidised bed and static bed drying techniques. It is clear that there is a significant difference in the nature and quality of these pellets and that the slower water removal associated with the static bed drying appears to cause some solute migration during drying and impaired surface smoothness.

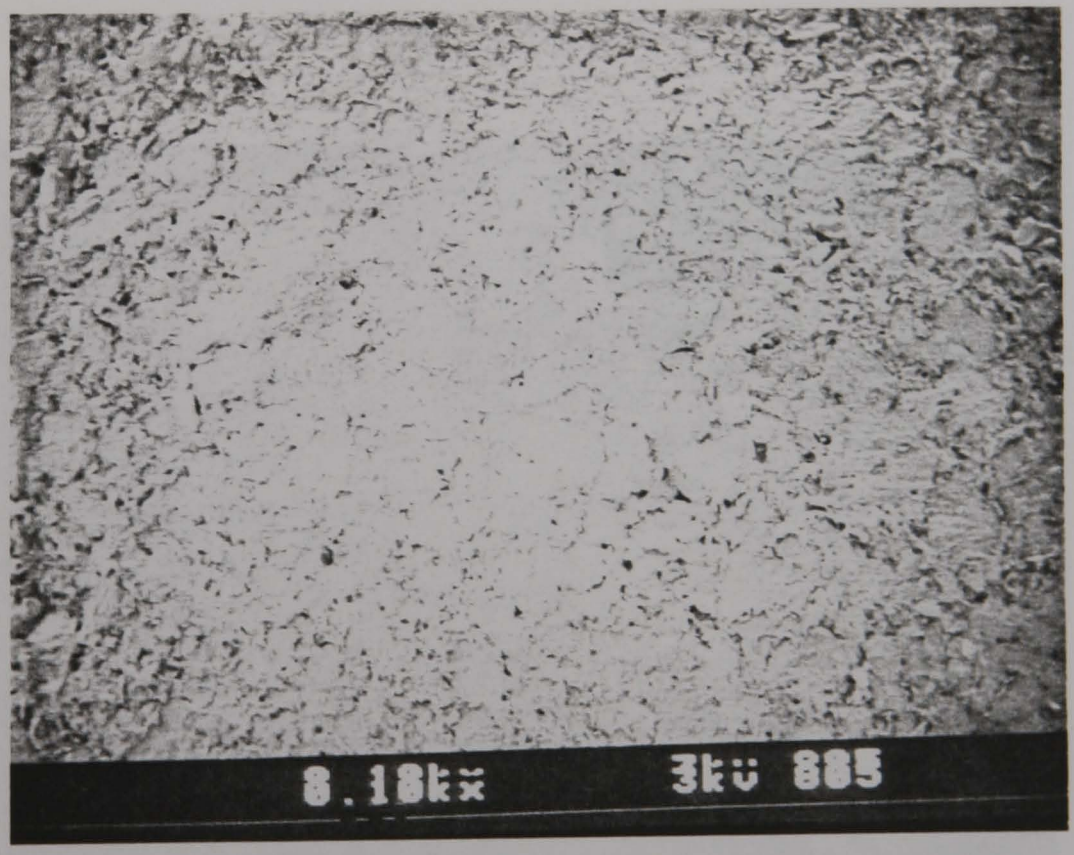


Figure 2.18a. SEM of an uncoated pellet surface dried by fluidised bed methodology; magnification x400.

Figure 2.18b. SEM of an uncoated pellet surface dried by tray drying; magnification x400.

Figure 2.19a. SEM of an uncoated pellet surface dried by fluidised bed methodology; magnification x800.

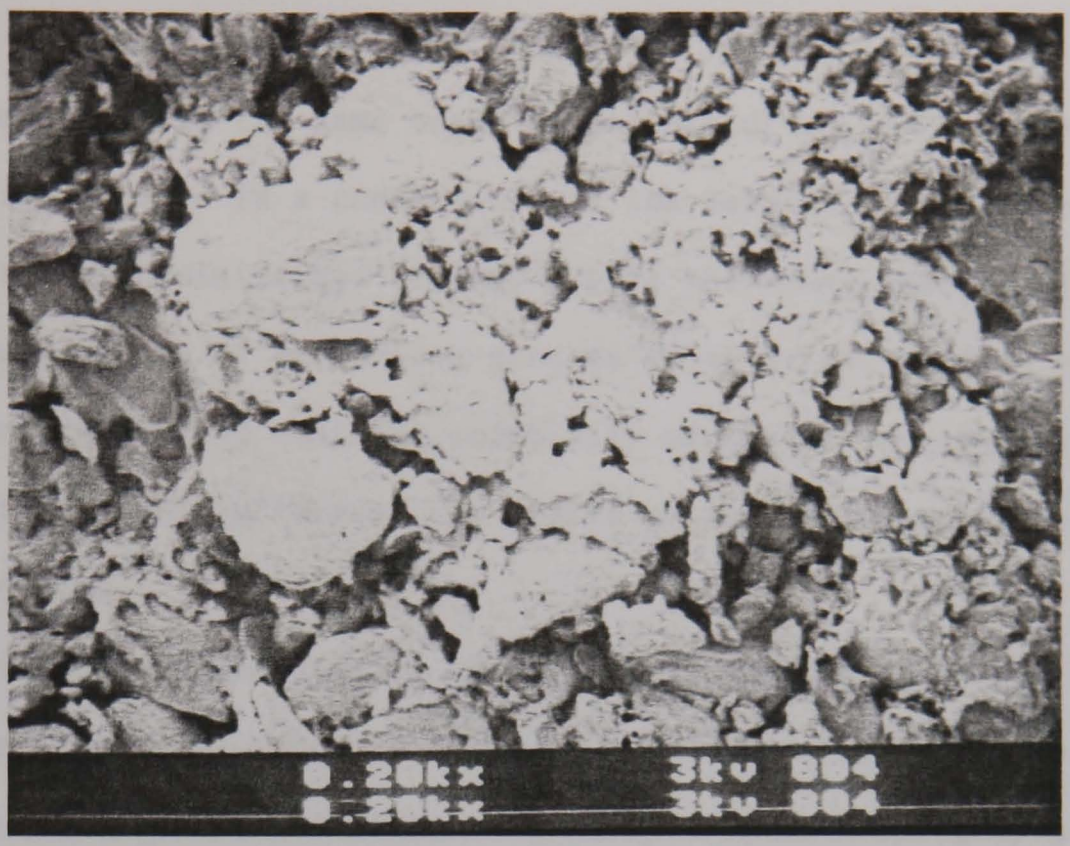


Figure 2.19b. SEM of an uncoated pellet surface dried by tray drying; magnification x800.

2.3.5.3. Effect of drying method on the diametral strength and elasticity of uncoated pellets.

Detailed consideration is given to the effect of the drying method on the tensile properties of uncoated pellets in section 6.3.2 of Chapter 6; pellets containing highly water soluble and poorly water soluble components are discussed. In summary, pellets dried using static bed techniques exhibit greater diametral strength and are less elastic than their fluidised bed dried counterparts.

2.4. Conclusions.

This work has revealed that for a given pellet formulation, the drying method employed has a significant effect on the mechanical strength of pellets prepared by extrusion-spheronisation. Pellets dried by tray drying exhibit greater diametral strength and skeletal density

and are less elastic than their fluidised bed dried counterparts.

In-vitro drug release from tray dried pellets is slightly enhanced when compared with the same batch of pellets dried by fluidised bed methodology. This is a consequence of the lengthy drying time which is associated with static bed drying. It is therefore postulated that it is the actual length of the drying process which is the primary cause of any solute migration and that the solubility of the pellet components in the granulating fluid influences the degree of solute migration occurring during drying.

A further consequence of the effect of the drying method and therefore the rate of the drying process on uncoated ibuprofen pellets is on the surface characteristics. Scanning electron micrographs have illustrated the effect of a lengthy drying process and solute migration on the quality of the surface smoothness of uncoated multiparticulates. This has ramifications in respect of the suitability of tray dried pellets for the subsequent application of a polymeric membrane or film coating. Particles prepared using this technique are well documented as possessing the ideal qualities necessary for the application of a release retarding membrane due to their uniform shape, particle size distribution and smooth surface characteristics.

It should also be noted therefore in addition to the many processing variables which are capable of significantly influencing the nature and quality of the final product, that the drying technique employed as a pelletization process variable will therefore influence the surface characteristics of pellets which may have consequences in respect of the suitability of such material for film coat application.

Figure 2.20 shows that the drug release from uncoated pellets is not sufficiently retarded to enable drug delivery over a 12 or 24 hour period and it was therefore considered necessary to apply a release controlling membrane to the uncoated pellets.

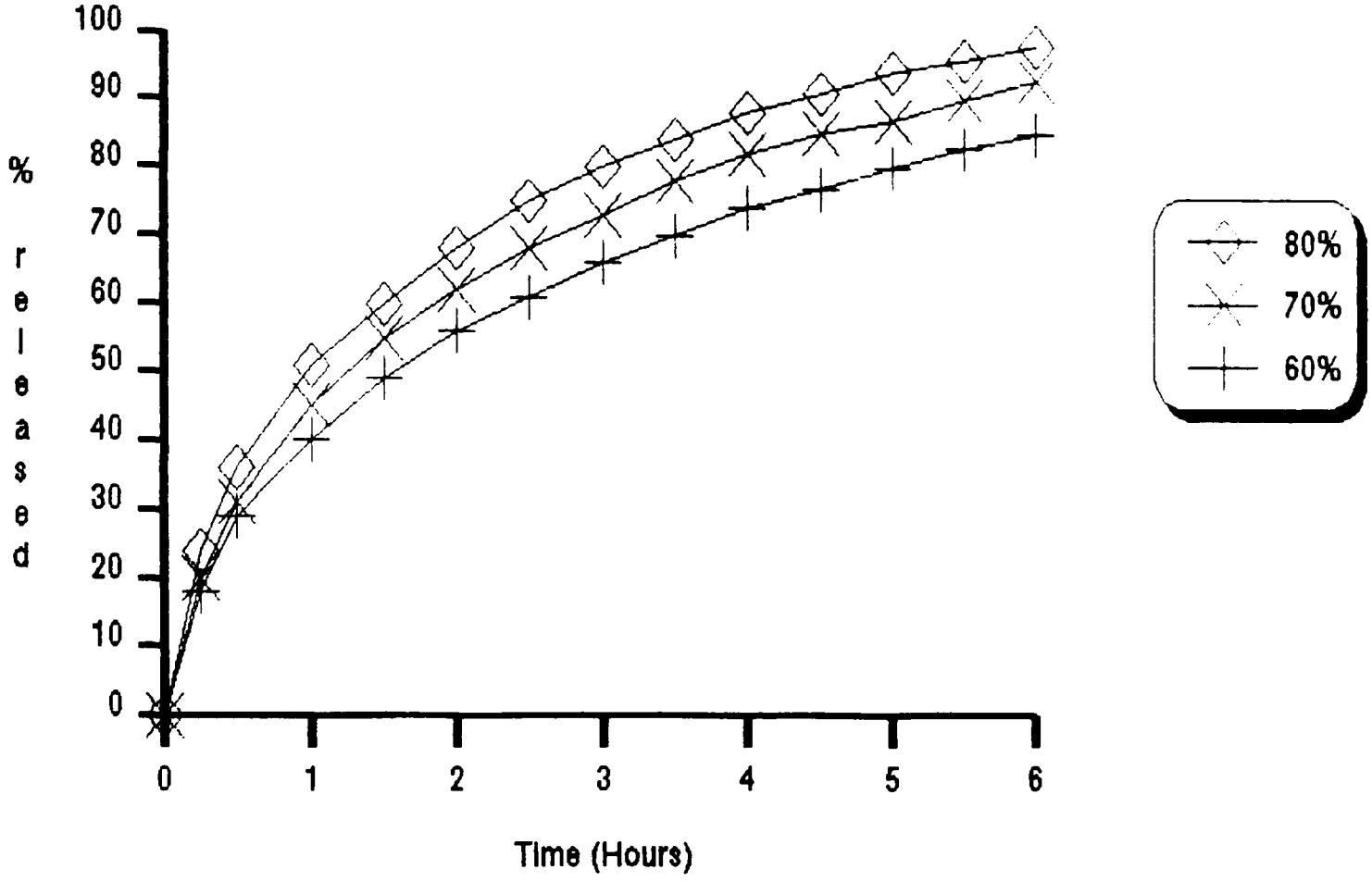


Figure 2.20. *In-vitro* drug release from uncoated pellets containing x %w/w ibuprofen with Avicel PH101 (see key).

It was postulated that the effect of the presence of a film coating would not only influence the drug release characteristics from these multiparticulates but that it may also impart additional mechanical strength. This scenario was considered to be highly favourable since these particles were required to retain their integrity following compaction into tablets.

Chapter 3 therefore is a study of polymer systems which were considered suitable for application to multiparticulates. The films are examined in terms of their effect on drug release from pellets containing ibuprofen (Chapter 4), the mechanical properties of free-films are studied in Chapter 5 and the effect of the presence of a film coating on the mechanical properties of pellets is studied in Chapter 6.

CHAPTER 3

STUDY OF SOME AQUEOUS POLYMERIC FILM COATING DISPERSIONS FOR APPLICATION TO IBUPROFEN PELLETS

3.1. Introduction.

Environmental pollution, flammability, explosion potential and the expense of flame-proofing equipment, are some of the disadvantages associated with the use of organic solvent systems for film coating. The possibility for solvent recovery exists, however the expense of installing such equipment is considerable; other problems include the purchase, quality control and storage of organic solvents.

Perceived advantages associated with the use of organic film coating solutions include the very rapid processing times which are possible with these systems. In reality however there is little difference in the total processing times associated with organic and aqueous systems. One of the main problems associated with aqueous systems is the sheer volume of water which must be removed by evaporation and its high latent heat of vapourisation. It is vital that a compromise product temperature is achieved during processing, such that the rate of heat energy input enables a steady product temperature to be maintained during water evaporation. Any increase in the outlet temperature during coating indicates either an excessive inlet temperature or an inadequate spray rate. This may result in premature drying of atomised droplets with resulting poor film quality. A decrease in the inlet temperature during processing indicates an excessive spray rate causing overwetting of the pellets, or alternatively a decrease in the inlet temperature. Due to the physical size of pellets any overwetting of the product due to excessive spraying or inadequate inlet temperature, is rapidly illuminated in the form of pellet agglomeration. This leads to an uneven distribution of polymer on the pellet surface and product agglomeration resulting in poor fluidisation of individual particles.

It was thought previously that the penetration of water into the core formulation during coating using aqueous systems would be a significant problem causing both physical damage to the dosage form and

chemical damage in the form of degradation of the active ingredient(s). This scenario however is avoidable by pre-warming the uncoated product prior to the application of the film coating dispersion.

Higher processing temperatures are possible with aqueous systems with little risk of causing thermal damage to the product, since much of the heat energy in the drying air is used to supply the latent heat of evaporation of the water and not in causing an excessive bed temperature.

Most water-insoluble polymers (including ethylcellulose and the polymethacrylates) may be presented in the form of a latex or pseudolatex dispersion in water. The need for organic solvents therefore is totally eliminated. Aqueous dispersions have low viscosities as compared to organic solutions with a comparable solids content and they are capable of containing a relatively high solids content.

Film formation in an organic solvent coating system depends on the polymer molecules becoming entangled and in close proximity to each other as the solvent is evaporated. Film formation in a latex system however relies upon the evaporation of water causing the latex spheres to soften, come within close proximity of like particles and then coalesce and deform to form a continuous film by capillary force and the surface tension of the polymer (Bindschaedler et al. 1983). The heat energy within the inlet air provides the energy necessary to evaporate off the aqueous phase and it also facilitates the softening and coalescence of the latex particles. Due to the low affinity of these latex particles for water relatively low operating temperatures enable efficient water removal. The actual drying temperature in the coating system is critical in the process of latex softening and particle coalescence. A continuous film is produced only if the temperature of the bed exceeds the minimum film-forming temperature (MFT). Conversely, if the product temperature is too high, particularly for small particles (pellets or granules), there may be the generation of an electrostatic interaction and

agglomeration as a result of excessive drying and softening of the latex film. The minimum film forming temperature should therefore be used as a guide for determining the air inlet temperature.

The volume of the fluidising air must be carefully controlled to produce efficient bed fluidisation. The spray rate of the coating dispersion affects the degree of wetting and the size of the atomised droplets (Hogan, 1982). Increasing the spray rate at a given atomisation pressure results in larger droplet formation and enhanced possibility of overwetting. The atomisation pressure must remain constant throughout the coating process as this influences the spraying pattern and the size of the droplets (Mathur et al. 1984). Excessive atomisation may result in disturbance of the fluidised bed, with possible attrition or damage of the particles and the loss of coating excipients by film formation on the chamber wall of the fluidising column. Inadequate atomisation is causative of overwetting of pellets and subsequent adhesion of pellets to themselves (agglomeration) and to the coating chamber wall.

The dynamics of the coating process is a carefully balanced equilibrium and is summarised in Table 3.1.

A key to achieving a smooth uniform polymeric coating on small particles using aqueous dispersions is the choice of the processing equipment and the conditions within the coating chamber. Equipment used for film coating may be classified into three basic groups; pans, perforated pans and fluid-bed processors (McGinity, 1989).

Basic requirements of the coating apparatus are that the materials being coated are contained in an environment which will enable the coating to dry. It must also be in an environment in which all particles receive equal amounts of evenly applied coating material and the same exposure to the drying conditions. The coating material must be delivered in a controlled and reproducible manner.

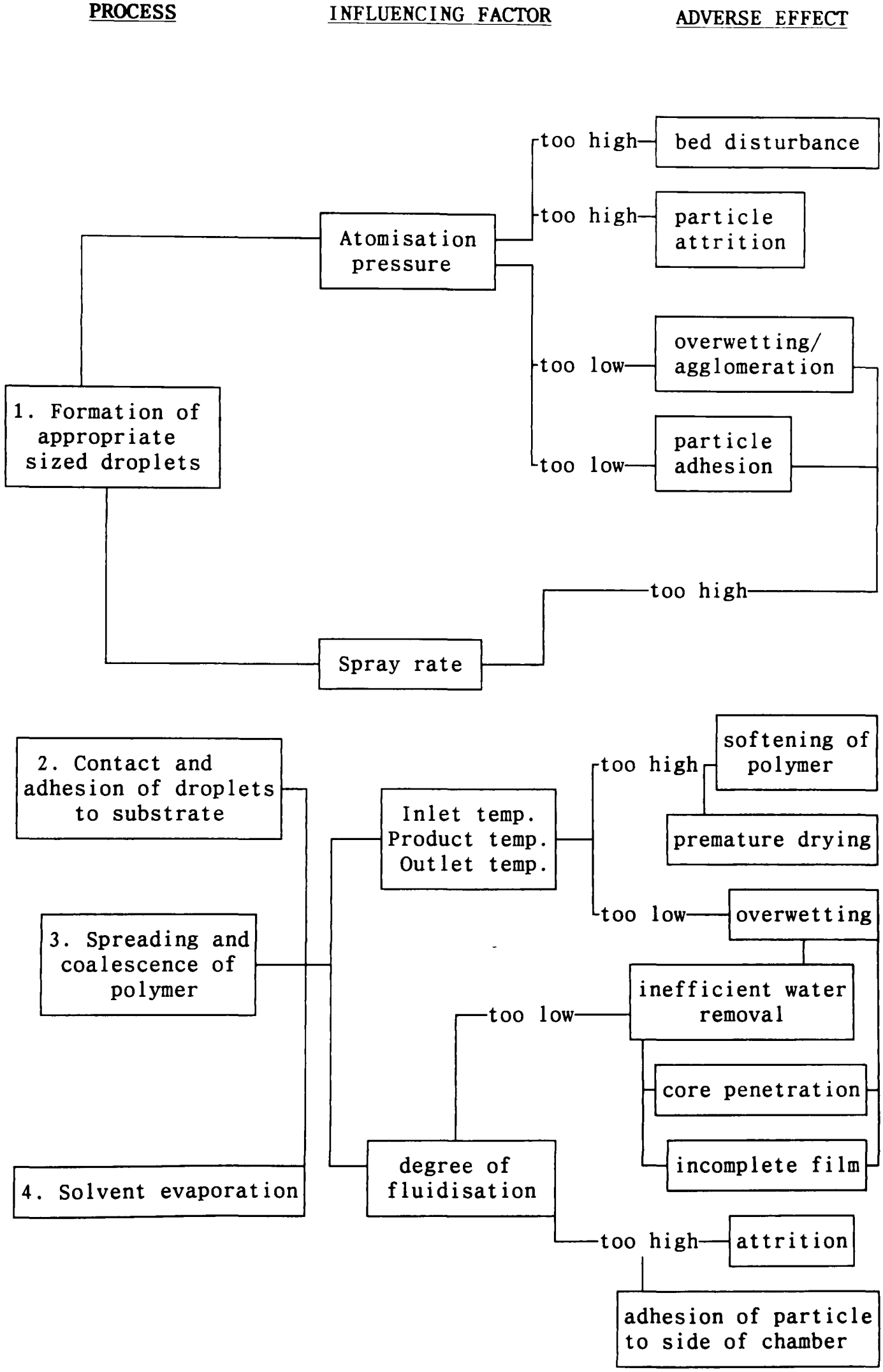


Table 3.1. Factors affecting the film coating process.

The conventional coating pan is used primarily for sugar coating. The perforated pan was developed to improve drying efficiency during the coating process by drawing air through the bed rather than supplying it to the bed surface only. These pans are not considered suitable for the application of sustained or controlled release coatings.

Fluidised bed apparatus provides the technique of choice for the coating of small particles using aqueous polymeric dispersions. Coatings may be applied to fluidised material as a spray either from above the bed, below or tangentially. Top spraying is the preferred method for the application of Eudragit Aqueous Dispersions (personal communication Röhm Pharma, Weiterstadt, Germany) since an even coating may be achieved with easy nozzle access during the coating process should a blockage occur. The pellets are fluidised to the height of the nozzle which sprays countercurrently into the material. High particle velocity and efficient heat transfer allow aqueous coating of small particles with little or no agglomeration under optimised coating conditions.

Bottom spray coating systems enable a quality product to be achieved although an inherent disadvantage of this system is the inability to access the nozzle during processing. Würster systems use a controlled air flow pattern formed by a partition and orifice plate. This method enables the application of droplets to the substrate prior to any significant evaporation of the vehicle; the surface solvent is then rapidly removed prior to core penetration. This method is considered suitable for the application of aqueous dispersions.

Mehta (1986) considered that the spray rate is probably the most important consideration in the aqueous film coating process. Film coating requires uniform application of the film and a controlled drying environment. This occurs simultaneously but independently during the coating process. The rate of heat transfer affects the rate of evaporation of the water and also for aqueous dispersions regulates the

rate and degree of coalescence of the polymeric material. In summary the ideal inlet air temperature enables an equilibrium to be established between the application of liquid and its subsequent evaporation, film formation and particle coalescence. If the product temperature, degree of fluidisation of the bed and the humidity of the inlet air are maintained constant, together with the dispersion spray rate, then the temperature and the humidity of the exhaust air will also remain constant. A state of equilibrium is achieved shortly after the commencement of film coating. In conclusion the critical coating process variables are listed below:

- spray rate
- atomisation pressure
- inlet air temperature
- degree of fluidisation of bed
- batch size
- outlet (exhaust) air temperature
- bed (product) temperature
- type of equipment
- method of spraying
- spray gun nozzle diameter
- delivery tubing diameter
- drying time

3.1.1. Polymethacrylates.

3.1.1.1. Chemical Structure.

The two products used in this study were Eudragit RS30D and RL30D (Röhm Pharma GMBH); both are methacrylic ester co-polymers and are insoluble in water, dilute acid, buffer solutions and digestive fluids.

Table 3.2 gives an indication of the characteristics of the two forms of polymethacrylates being studied. (Source: McGinity, 1989).

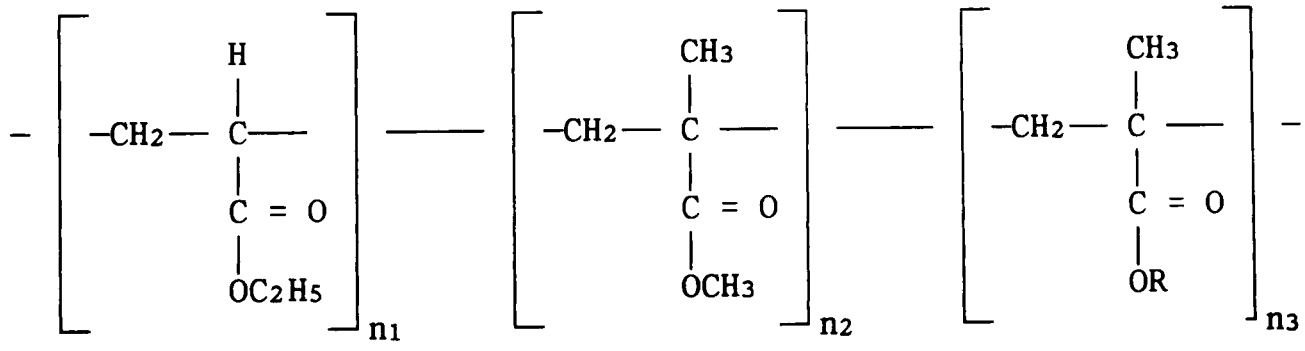
Both Eudragit RS30D and RL30D commercial dispersions contain 30%w/w polymer with 0.25%w/w sorbic acid added as a preservative. The MFT of these dispersions is 40-50°C. Addition of 10-20%w/w plasticiser reduces the MFT to below 20°C.

Commercial name	Marketed as:	Behaviour in digestive juice	$n_1:n_2:n_3$ (see below)	MW (Da)
RL30D	30%w/w aqueous dispersion	insoluble film high permeability	1:2:0.2	150,000
RS30D	30%w/w aqueous dispersion	insoluble film low permeability	1:2:0.1	150,000

Table 3.2. Relative properties of Eudragit RL30D and RS30D.

Scientific name : poly(ethylacrylate, methylmethacrylate) trimethyl-ammonioethyl methacrylate chloride

Structural formula :



(R: $CH_2-CH_2-N^+(CH_3)_3\ Cl^-$)

3.1.1.2. Processing considerations.

Prior to the application of the aqueous dispersion to the product it is necessary to pre-warm the bed to enable satisfactory film formation under the desired mild operating conditions.

When the temperature of the product is approximately 10-20°C above the MFT and the drying capacity of the inlet air is sufficient to enable rapid drying, the first latex layer immediately forms a thin water-insoluble film; this prevents penetration of the aqueous phase into the

core of the product. For an uncoated formulation which is highly water-sensitive it may be necessary to pre-coat the cores using an organic coating system.

Table 3.3 shows the minimum film-forming temperatures for Eudragit RL and RS as aqueous dispersions with added plasticiser.

	EUDRAGIT			
	RL		RS	
Quantity of plasticiser*	10%	20%	10%	20%
No plasticiser	39	39	47	47
Triethylcitrate	11	<0	20	5

* plasticiser expressed as % weight dry polymer

Table 3.3. Effect of plasticiser on the MFT for Eudragit aqueous dispersions. (Source: McGinity, 1989).

The MFTs of the pure dispersions are approximately 40 and 50°C respectively. As previously mentioned it is necessary to add 10-20%w/w plasticiser to reduce the MFT to below 20°C. The literature reports that one of the most effective plasticisers is triethylcitrate; this is the plasticiser most recommended for use in these systems by Röhm Pharma (personal communication).

3.1.2. Ethylcellulose.

Ethylcellulose in the form of Surelease, a commercial aqueous polymeric dispersion containing incorporated plasticiser, is studied. This product contains 17.5%w/w polymer (70% of the total solids content); the total solids content being 25%w/w (Ghebre-Sellassie et al. 1988). The plasticisers in this product are a combination of dibutyl sebacate and oleic acid such that the plasticiser molecules are incorporated within the dispersed polymer particles. The manufacturers claim that

this enables film coalescence during the coating process and is discussed subsequently.

Other excipients include the vehicle ammoniated water, which serves to stabilise the dispersed polymer and fumed silica as an antiadherent. The latter facilitates the application of Surelease during the actual coating process.

With this particular coating system, the manufacturers recommend that following the application of the release controlling membrane, it is necessary to apply an overcoat formulation to the product in order to minimise interparticulate adherence. The overcoat formulation consists of a solution of Opadry Clear (YS-1-7006) in purified water BP. The component excipients the Opadry are HPMC, PEG 400 and PEG 6000. Although the overcoat formulation is extremely viscous this work has shown that it is an absolutely essential part of this coating system since there is a high tendency of pellets coated solely with the Surelease dispersion to agglomerate. Furthermore the overcoat formulation imparts free-flow characteristics to pellets coated in this manner. The manufacturers literature states that conditions within the coating chamber should be maintained such that the outlet temperature is within the range 24-30°C. Film formation is achieved during the coating process only if the drying conditions within the chamber are as indicated and the MFT is exceeded; this enables coalescence of polymeric particles to occur simultaneously with film coat application. A working equilibrium is rapidly established during the coating process and must be maintained throughout in order that complete film formation may be achieved.

3.1.2.1. Chemical Structure.

Ethylcellulose, empirical formula

$$C_{12}H_{23}O_6(C_{12}H_{22}O_5)_{n-2}C_{12}H_{23}O_5$$

consists of the cellulose molecule as a chain of β-anhydroglucose units joined together by acetal linkages. Ethylcellulose is water insoluble.

3.1.2.2. Processing considerations.

Porter (1989) describes the heat generated by the coating process as important in facilitating the coalescence of the polymer particles on the surface of the dosage form. Porter also indicates that should the polymer coated product be exposed to elevated temperatures then some softening of the membrane may occur causing "clumping". Porter states that this problem is eliminated by the application of an aqueous overcoat formulation to the polymer coated product. This present work has confirmed that an overcoat formulation is necessary to prevent coated particles from adhering to each other and not only at elevated temperatures. Ibuprofen pellets coated with Surelease showed complete agglomeration following coating even after cooling to room temperature. This problem was successfully eliminated by the presence of the overcoat formulation, quantitative details of which are discussed in section 3.2.

The type of polymer system applied to the surface of the pellets is a major factor influencing the drug release characteristics. The nature of the film coat is determined largely by the polymer used, but also the presence of other excipients within the coating dispersion. Ethylcellulose aqueous dispersions require the presence of plasticiser to enable complete film formation by facilitating polymeric particle coalescence. Colorcon have incorporated the appropriate level of plasticiser into their commercial preparation during the manufacturing process.

The importance of plasticiser incorporated into ethylcellulose aqueous dispersions is discussed by Goodhart et al. (1984). Since the latex forming process involves the fusion of individual polymer particles to form a continuous membrane, sufficient plasticiser must be present to

cause a lowering of the MFT, thus enabling polymer particle coalescence and deformation under the operating conditions of the coating chamber. The basis for film formation is therefore attributable to the capillary pressure exerted by the closely packed polymer particles as a result of water evaporation (Goodhart et al. 1984). Plasticisers enhance polymer pliability; in latex systems however they must also enable particle coalescence by reducing the glass transition temperature (Tg) or MFT. Assuming that polymer coalescence and film formation is complete, the drug release rate from a polymer coated product is a function of the plasticiser concentration in addition to the thickness of the polymeric membrane surrounding the individual particles.

Ozturk et al. (1990) reported that plasticiser is important with respect to forming a continuous film and that diffusion of drug through the plasticiser channels is unlikely to make a significant contribution to the overall drug release rate. The authors also indicate that for pellets coated with an ethylcellulose pseudolatex plasticised with dibutyl sebacate, lowering the amount of plasticiser increases the drug release rate dramatically. This relatively faster drug release observed at low plasticiser levels was shown by SEM studies to be attributable to major flaws in the film; thus indicating that there is a minimum level of plasticiser required for these ethylcellulose based systems necessary for continuous and complete film formation.

Lippold et al. (1990) state that plasticised aqueous ethylcellulose dispersions show a decrease in the MFT from 87°C to approximately 30°C with 20% dibutyl sebacate in the resulting film. They also state that the plasticiser must completely penetrate the ethylcellulose particles prior to film formation in order that optimal film formation is achieved.

The film formation of ethylcellulose from an aqueous polymeric dispersion is described by Porter et al. (1989). In the dispersion, the polymer is present as discrete particles in an aqueous vehicle.

Film formation requires that these polymeric particles come into close proximity with each other enabling polymer deformation and fusion in the from of coalescence. Simultaneously the aqueous vehicle is removed. The coalescence of these polymeric particles is facilitated by the capillary forces between them being generated as the water is driven off by evaporation. Porter also states that coalescence can only occur completely as a result of viscous flow, thus eliminating the boundaries between adjacent polymer particles. Therefore diffusion of polymer chains must occur across the boundaries; this process may be accounted for to some extent by the free volume theory which presumes that sufficient free volume or intermolecular space exists in the bulk polymer to accommodate the diffusion process.

The glass transition temperature (Tg) of ethylcellulose is reported to be 135°C (Rowe et al. 1984). Since the Tg of ethylcellulose is significantly greater than the temperature used during the coating process in the application of these aqueous dispersions, the system must be efficiently plasticised to enable complete coalescence of the latex particles and the formation of a continuous film. The authors also indicate that by lowering the glass transition temperature of the polymer, the toughness of the ethylcellulose film should be greatly improved, thus enabling the film coat to withstand stresses occurring during the coating process more easily and ultimately such that these polymer coated pellets may withstand compression with no impaired integrity of the film coat and hence the drug-laden multiparticulates.

Ghebre-Sellassie et al. (1988) reported that the occurrence of complete film formation achieved during coating depends upon the manufacturing processes, the coating conditions and the formulation variables used; they also state that an additional curing step may be necessary. These authors comment that it is highly probable that the incorporation of plasticiser during the manufacturing process of

Surelease results in some interaction between the plasticiser and the polymer particles; this causes the polymer particles to swell and partially deform during the coating operation. Furthermore this interaction may not be great enough to provide the necessary degree of softening of these polymeric particles at temperatures of between 28°C and 40°C, thus ensuring complete coalescence. These authors conclude by saying that in order to ensure the stability of the coating during storage and handling over a range of temperatures, Surelease coated actives must be cured at elevated temperatures.

To be effective a plasticiser molecule must interpose itself between the polymer chains and interact with the forces holding the chains together, thereby extending and softening the polymer matrix (Rowe, 1982). The mobility of a polymer chain influences the magnitude of the stresses due to shrinkage. Plasticisers increase the polymer chain mobility and therefore have a significant effect on those stresses and hence the incidence of film cracking; non-plasticised are therefore more brittle than plasticised films.

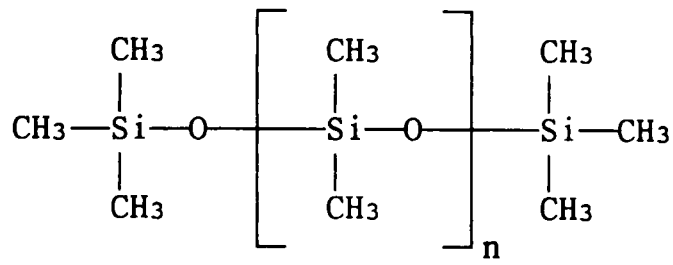
In summary therefore, it is the shrinking of the water film around the latex particles which produces a surface tension high enough to drive the polymer particles close together. Film formation then occurs by coalescence as the boundaries between the latex particles disappear. Coalescence is facilitated by the presence of incorporated plasticiser which is capable of diffusing itself into the latex pellets resulting in a softening effect. The reduction in the MFT enables continuous film formation under the operating conditions of the coating process. It may be necessary to complete the coalescence by means of a curing process following coating.

3.1.3. Silicone Elastomer.

3.1.3.1. Chemical Structure.

The Dow Corning X7-2837 Silicone Emulsion is polymerised latex and is a cross-linked product of hydroxyendblocked polydimethylsiloxane (PDMS). When this material is combined with colloidal silica particles and a water dispersible organic material, an aqueous latex dispersion results which may be used as a controlled release system for oral dosage forms.

The chemical structure of polydimethysiloxane (PDMS) is shown below:



The formulation for the controlled release system being studied is composed of the silicone elastomer latex, colloidal silica and a plasticiser, polyethylene glycol; although Dow Corning do suggest that the incorporation of a plasticiser may not be necessary for the coating of small particles or pellets using this coating system (personal communication). The use of a plasticiser in silicone elastomer film formulations is discussed subsequently in section 3.2.3.

The silicone latex X7-2837 has a mean particle size of 200nm, a pH of 8.2 and a total solids content of 53.0%w/w. The colloidal silica is a silica sol with a mean particle size of 4nm, a pH of 10.7 and a solids content of 17.0%w/w.

3.1.3.2. Processing considerations.

Li and Peck (1989) have studied controlled release tablets coated with a silicone elastomer membrane. The suitability of this system for controlled release coating is primarily dependent upon the permeability

of the coating to various drug molecules. Polydimethylsiloxane is hydrophobic in nature and therefore the silicone elastomer membrane is relatively impermeable to hydrophilic and ionic compounds. Incorporation of water soluble components within the hydrophobic silicone elastomer formulation in the form of the polyethylene glycols has been shown to enhance the drug release from dosage forms coated with this system (Li and Peck, 1989).

The fundamental film properties are determined largely by the nature and quantity of the excipients from which they are composed. Li and Peck (1989) have studied free-films derived from silicone elastomer aqueous dispersions with particular reference to the level and type of plasticiser and to the ratio of silicone to colloidal silica forming the latex. They have generated information relating to the elasticity and mechanical strength of free-films, including tensile strength and elongation at break; both factors of which are of considerable importance in the design of a coating system which will withstand compression and enable the coated pellets to retain their integrity.

Li and Peck speculated that the presence of polyethylene glycol (PEG) in the silicone elastomer film facilitates the formation of a porous film structure in an aqueous medium, through which the hydrophilic and ionic species pass as they are leached from the core of the dosage form. Furthermore, that the presence of different molecular weight PEGs may be an effective formulation variable and a means of controlling the rate of drug release. Personal communication with Dow Corning however suggests that for small particles, the use of a plasticiser may not be necessary. Data presented by these authors indicates that with increasing silicone to silica ratio, there is a reduction in the elastic modulus and a marked increase in the percentage elongation for free films. With increasing silica content however the film becomes correspondingly more brittle.

The work of these authors supports the idea that at low loading levels the incorporation of PEG as a plasticiser in silicone elastomer mixed films, leads to reduced brittleness and a corresponding ductility associated with the silica filled silicone elastomer. This plasticising effect it is suggested may be attributed to the polar interaction between the polymer and the silica. At high plasticiser levels however, the plasticising effect of the PEG is prevented due to the presence of unbound PEG causing an apparent film brittleness. Li and Peck (1989) also indicated that complete leaching of PEG(s) from these silicone elastomer films and extensive film hydration in water, causes these silicone elastomer films to exhibit a highly porous structure which may provide water filled diffusion channels for the leaching out of polar or ionic molecules.

In addition Li and Peck (1989) studied drug release from potassium chloride tablets coated with silicone elastomer controlled release coatings. Significant formulation variables were found to include the loading level and the molecular weight of PEG and the ratio of silicone to silica in the coating dispersion. Other variables were shown to alter the drug release rate from coated tablets, including drying temperature, pH of the dissolution medium and aging. Furthermore these authors showed that the PEG molecular weight has a greater effect on the drug release rate than the ratio of silicone to silica. Tablets coated with a low silicone to silica ratio released potassium chloride at a faster rate than those with a higher silicone content. An increased silicone to silica ratio it is reported, produces a more compact coating with a microporous tortuous structure than a film coating containing a lower level of silicone.

A study is made in this present work of the effect of the silicone to silica ratio and the presence of PEG on the drug release from ibuprofen pellets and also of the elastic properties of free-films of

these silicone elastomer formulations. SEM studies have been performed on coated material and also on coated pellets from which drug has been removed by *in-vitro* dissolution testing.

3.2. Materials and Methods.

Three polymeric aqueous dispersion coating systems were studied and are discussed accordingly. The use of the different systems was designed to enable evaluation of the three polymers with respect to their effect on drug release, their relative mechanical strengths and elasticities and ultimately the ability of the coated pellets to retain their integrity following compression into tablets with an inert diluent formulation.

The information appearing in Table 3.4 relates to the excipients used in the manufacture of the film coating dispersions and the source from which they were obtained.

3.2.1. Polymethacrylate (Eudragit) aqueous polymeric dispersions.

3.2.1.1. Formulation.

Eudragit RS30D and Eudragit RL30D were used in combination such that the resulting polymeric membrane was the factor controlling the drug release rate rather than the quantity of plasticiser incorporated within the film coat. The RS30D exhibits low permeability but when in combination with the highly permeable RL30D, a satisfactory release profile is obtained. To this end 20%w/w triethylcitrate (Citroflex 2) was included as an integral part of the formulation. This level of plasticiser is documented as reducing the MFT to 5°C, thus ensuring complete film formation during the coating process (McGinity, 1989). For the purpose of calculation plasticiser is expressed as per cent weight of dry polymer (see Table 3.3, section 3.1.1.2).

Excipient	Supplier
Eudragit RS30D & RL30D	Röhm Pharma GMBH Weiterstadt, Germany
Citroflex 2 (triethylcitrate)	Pfizer Ltd., Chemicals Div., Sandwich, Kent
Syloid Silica 244FP	Grace GMBH, Postfach 449, Worms, Germany
Surelease Dispersion	Colorcon Ltd., Murray Road, St. Pauls Cray, Orpington, Kent
Opadry (YS-1-7006)	Colorcon Ltd.
Silicone Emulsion	Dow Corning Company France
Colloidal Silica	Dow Corning Co.
PEG 6000 BP	Boots Pharmaceuticals

Table 3.4. Excipients used in film coating studies and their suppliers.

Syloid Silica 244FP is included in the formulation to aid the coating process as an anti-adherent or anti-tack agent. It has an average particle size of 3μm and a specific surface area of $310m^2\ g^{-1}$ and is therefore an ideal excipient offering an efficient means of minimising the tendency for agglomeration or sticking of particles within the coating chamber, assuming of course that the processing variables are optimised as previously discussed. Table 3.5 gives quantitative formulae for the Eudragit aqueous polymeric dispersions; the coating formulation contains 13.35%w/w polymer solids.

It is an aim of this work to study the effect of polymer level on the drug release rate, paying particular regard to the mechanical and physical properties of coated pellets, rather than a study of the film coating composition about which much has been published and is discussed in section 3.1.

Excipient	%w/w	g polymer
Eudragit RS30D	35.5	10.65
Eudragit RL30D	9.0	2.7
Citroflex 2	2.67	-
Syloid Silica 244FP	4.0	-
Purified water BP	48.83	-
	100.00	13.35

Table 3.5. Quantitative particulars of the polymethacrylate aqueous dispersion used in film coating studies.

3.2.1.2. Method of manufacture.

Citroflex and Syloid were added to the purified water and mixed at low shear for 5 minutes. In a separate container the Eudragit RS30D was added to the Eudragit RL30D with stirring. The aqueous solution was then added to the polymeric dispersion and mixed with low shear for a further 5 minutes. Agitation in the form of low shear mixing was maintained throughout the coating process; excessive agitation causes frothing and increases the risk of dispersion coagulation.

Uncoated pellets (500g) were placed in a 1kg Aeromatic Fluidised Bed Dryer (Strea 1) with top spray attachment. It was found necessary to use a stainless steel chamber for coating of small particles since generation of static during product pre-warming rendered satisfactory fluidisation of pellets impossible within a perspex chamber.

The spray gun had a liquid nozzle diameter of 1.10mm and the film coating dispersion was applied by means of a peristaltic pump and 2mm bore diameter silicone tubing. Röhm Pharma suggested that the use of tubing of diameter in excess of 2mm leads to sedimentation of the solid components forming the dispersion during transit from the bulk container to the nozzle of the spray gun attachment.

Pellets were fluidised to nozzle height and pre-warmed to a product temperature (represented by the outlet temperature) of 28-32°C and a

inlet temperature of 50°C. The product temperature did not exceed 40°C during the coating process; temperatures in excess of this cause polymer softening and as a consequence, sticking and agglomeration of the product both to itself and to the coating chamber during the coating process.

A spray rate of approximately 10g min^{-1} kg^{-1} product and an atomisation pressure of 2 bar was found to be optimum and maintained throughout. The film coating dispersion was applied by weight and the coating application spraying times recorded to ensure a constant spray rate. Accordingly visual observation of the product within the coating chamber and the outlet temperature gives an accurate indication of the success of the coating procedure during processing.

500g batches of uncoated ibuprofen pellets were coated with progressively increasing polymer loadings and are expressed as percentage increase in weight of product. Plasticiser is expressed as per cent weight dry polymer for the purpose of calculation of solids content of the dispersion, therefore the formulation in Table 3.5 contains 20%w/w solids. Eudragit RS30D and RL30D both contain 30%w/w polymer and the aqueous dispersion contains 13.35%w/w polymer.

For each given uncoated pellet formulation, small samples of coated product were removed from the batch during the coating process. Just prior to sample removal, the batch was subjected to an interim 10 minute drying period under the drying conditions already established within the system. For all batches of coated pellets, the following procedures were adhered to:

i) pre-warming of the bed to approximately 30°C

ii) atomising pressure of 2 bar

iii) uncoated batch size of 500g

iv) post-coating drying for 30 minutes under existing drying conditions

v) post-coating drying for 24 hours at 40°C in a hot air oven.

In order to ensure that the formation of a complete film was produced during processing, coated pellets were subjected to a period of 24 hours tray drying at 40°C. A control sample was also taken (a sample of pellets which were not subjected to this "curing" process). The *in-vitro* release profiles obtained for the aforementioned samples yielded information relating to the success of the plasticiser in reducing the MFT to below that temperature existing in the coating chamber, such that polymer particle coalescence and complete film formation was ensured during processing.

Table 3.6 is a summary of ibuprofen pellet formulations coated with the polymethacrylate aqueous dispersion.

% ibuprofen in cores	% weight increase	spray rate ($g\ min^{-1}\ kg^{-1}$)
80	12.0	8.36
80	4.5	12.16
70	9.2	9.12
70	5.3	11.32
60	5.6	8.84

Table 3.6. Summary of uncoated ibuprofen pellet formulations coated with the Eudragit aqueous film coating dispersion.

A study of the *in-vitro* release profiles (Chapter 4) enabled the selection of a suitable polymer loading. This study highlighted that it is possible with such coating systems to apply an accurate polymer loading to multiparticulates such that a specific *in-vitro* release profile is obtained; the greater the potency of the uncoated pellets, the greater the quantity of polymer was necessary to retard drug release. It is interesting that the 10% weight increase recommended by Röhm Pharma was far in excess of that necessary to produce the sustained drug release

of ibuprofen pellets over 24 hours. Details relating to *in-vitro* dissolution methodology and the drug release profiles of both uncoated and coated ibuprofen pellets appear subsequently in Chapter 4.

3.2.2. Ethylcellulose (Surelease) aqueous polymeric dispersions.

3.2.2.1. Formulation.

Commercially available Surelease Dispersion contains 25%w/w solids; the manufacturers recommend that the product be diluted to 15%w/w solids for application as an aqueous polymeric dispersion of ethylcellulose to oral dosage forms. It is necessary with this product to apply an overcoat formulation to product coated with the polymeric dispersion, in order to minimise and ideally eliminate sticking and adherence of particles to themselves and to the coating chamber walls and spray gun attachment. A weight gain of 1%w/w is sufficient the manufacturers claim, to impart free-flow characteristics to the polymer coated product. The film coating dispersion and overcoat formulation compositions being studied therefore are as follows:

Surelease Dispersion (15%w/w solids)	%w/w
Surelease Dispersion (25%w/w solids)	60.0
Purified water BP	40.0

Overcoat Formulation	%w/w
Opadry Clear (YS-1-7006)	10.0
Purified water BP	90.0

3.2.2.2. Method of manufacture.

The Purified water BP was added to the Surelease dispersion with low shear mixing and gentle agitation for approximately 15 minutes and then throughout the coating process; vigorous mixing resulted in excessive foaming. With the overcoat formulation, Opadry was rapidly added to the

vortex of Purified water BP, again under the conditions of low shear mixing. This mixing process was continued for not less than 45 minutes; the minimum time necessary for complete hydration and dissolution of the Opadry. The resultant product was that of a highly viscous gel-like solution which was also agitated gently throughout the coating process.

The apparatus and coating procedure are as described in 3.2.1.2. As previously discussed, uncoated pellets were pre-warmed to a bed temperature of 28-32°C.

Colorcon recommended a weight increase of 10%w/w; for the coating of small multiparticulates this polymer loading was again found to be excessive. Table 3.7 summarises those batches of pellets coated with ethylcellulose and the product weight increase associated with the film coating.

% ibuprofen in cores	% weight increase	spray rate (g min^{-1} kg^{-1})
80	10	11.10
70	10	12.10
70	7.5	12.82
60	10	13.60
60	5	12.38

Table 3.7. Summary of uncoated ibuprofen pellet formulations coated with Surelease.

In-vitro dissolution profiles (Chapter 4) indicated that a 10% weight increase delayed drug release to too great an extent for uncoated pellet cores containing 60% and 70% ibuprofen. Therefore additional batches of pellets were coated with 5% and 7.5% solids weight increases.

It is necessary with this product to apply an overcoat formulation to prevent sticking and particle agglomeration. An overcoat formulation

was therefore applied to each batch such that a further weight increase of 1%w/w was achieved. The resultant pellets were free-flowing with a smooth esthetically pleasing glossy outer coat. The coating level is expressed as %w/w solids applied to the uncoated material and is expressed as a percentage of the initial batch size.

A post-coating tray drying process (the so-called "curing" stage) was performed on pellets coated with Surelease Dispersion; 24 hours tray drying at 40°C. Again a control sample was taken and the *in-vitro* drug release profiles obtained. The effect of this "curing" stage on the quality of the films and *in-vitro* release profiles are illustrated and discussed in Chapter 4.

3.2.3. Aqueous polymeric dispersions containing Silicone Elastomer.

3.2.3.1. Formulation.

The Silicone Elastomer Emulsion is composed of a silicone elastomer latex and colloidal silica. It is optional whether plasticiser is incorporated within the product; this is discussed later. No work has been published to date regarding the use of this aqueous formulation of silicone elastomer and the film coating of pellets; the composition of the final emulsion with respect to the ratio of silicone to silica and the presence or otherwise of plasticiser, are obviously factors which require investigation.

Formulations containing silicone to silica ratios of 2:1, 4:1 and 6:1 were prepared and applied to ibuprofen pellets as aqueous polymeric film coating emulsions. Further work included a study of the effect of PEG 6000 10%w/w (polyethylene glycol 6000 BP) on the quality of the film coating; the effect of PEG on the coating process and drug release from ibuprofen pellets coated with these products. Although it was possible to coat pellets with an emulsion containing PEG 10%w/w (ratio 2:1) problems were experienced with interparticulate adhesion; it was found

necessary to increase the volumetric flow rate of the fluidising air in order that product fluidisation was maintained during coating. Incorporation of PEG in the 4:1 formulation however was unsuccessful. It was not possible to achieve a bed temperature which was low enough to prevent the waxy nature of this plasticiser from causing sticking and yet high enough to enable water evaporation during the coating process.

Li and Peck (1989) reported that film coating dispersions containing up to 40% PEG were feasible for the film coating of tablets. It must be assumed that these workers did not experience similar problems of adherence of particles to each other and to the walls of the coating chamber seen with pellets. It is assumed that this is due to differences in the physical characteristics and dimensions of tablets and pellets.

This work has shown that an increase in the silicone to silica ratio and the incorporation of PEG within the emulsion, increases the tendency for sticking and reduces the ease with which fluidisation is achieved and maintained throughout the coating process. These findings support similar observations made by the manufacturers in the literature provided with the product. The large surface area associated with multiparticulates appears to negate the need for incorporation of plasticiser within the polymeric film, since favourable release profiles are obtained in its absence.

In-vitro dissolution profiles (section 4.3.2, Chapter 4) illustrate the effect of the silicone to silica ratio and the presence of plasticiser on drug release from pellets containing ibuprofen.

Table 3.8 summarises those elastomer formulations studied and briefly highlights the success or otherwise of the film coating process.

Excipients	%w/w	% w/w solids	Silicone: Silica ratio	Comments
Silicone Emulsion Colloidal Silica Purified water BP	21.88 34.10 44.02	11.60 5.80 -	2:1	No PEG; coating process satisfactory
Silicone Emulsion Colloidal Silica Purified water BP	43.77 34.12 22.11	23.20 5.80 -	4:1	No PEG; coating process satisfactory
Silicone Emulsion Colloidal Silica Purified water BP	32.83 17.06 50.11	17.40 2.90 -	6:1	No PEG; coating process satisfactory
Silicone Emulsion Colloidal Silica Purified water BP	43.77 17.06 39.17	23.20 2.90 -	8:1	No PEG; some tendency for sticking
Silicone Emulsion Colloidal Silica PEG 6000 BP Purified water BP	21.88 34.10 10.00 34.02	11.60 5.80 10.00 -	2:1	10% PEG; coating process satisfactory
Silicone Emulsion Colloidal Silica PEG 6000 BP Purified water BP	21.88 17.06 5.00 56.06	11.60 2.90 5.00 -	4:1	10% PEG; severe pellet adhesion during coating
Silicone Emulsion Colloidal Silica PEG 6000 BP Purified water BP	32.83 17.06 5.00 45.11	17.40 2.90 5.00 -	6:1	10% PEG; total product agglomeration during coating

Table 3.8. Silicone Elastomer coating formulations studied.

3.2.3.2. Method of manufacture.

Colloidal Silica X7-2837(B) was added to the Silicone Emulsion X7-2837(A) and agitated with low shear mixing. Where present plasticiser was dispersed in the purified water and added to the emulsion, again with low shear mixing. Addition of the remaining water to the formulation again with stirring, completed the process. Gentle agitation was maintained throughout the coating process. The apparatus and coating procedure is described in 3.2.1. A weight increase of 10% was applied to pellets calculated based on the % solids within each coating dispersion.

For those batches in which plasticiser is present, PEG is considered to be contributing to the solids content of the dispersion. Hence for pellets coated with aqueous formulations containing plasticiser, there is a reduction in the level of polymer applied by virtue of the fact that plasticiser is displacing polymer in respect of the solids present within the dispersion (for example 50g of solids applied to 500g of uncoated pellets is equivalent to a weight increase of 10%w/w). In summary, 50g of solids were applied to the uncoated material irrespective of the presence of plasticiser in the dispersion. As with the polymethacrylate and ethylcellulose coated preparations, the polymer applied to pellets is expressed as the weight of coating solids applied as a percentage of the batch size of uncoated pellets.

Table 3.9 shows the quantities of silicone elastomer film coating dispersion applied to 500g batches of uncoated ibuprofen pellets. The uncoated pellet formulation used in this particular study contained 80%w/w ibuprofen.

ratio silicone:silica	% w/w solids	weight sprayed	spray rate g min^{-1} kg^{-1}
2:1	17.50	286g	12.88
4:1	20.30	246g	11.08
6:1	29.00	172g	10.48
6:1 (+ 10% PEG)	27.40	183g	10.48

Table 3.9. Summary of the coating variables for batches of ibuprofen pellets coated with Silicone Elastomer aqueous dispersions.

3.3. Results and Discussion.

Uncoated pellet cores containing 60%, 70% and 80%w/w ibuprofen were coated with aqueous polymeric dispersions of the polymethacrylates, ethylcellulose and silicone elastomer. For each coating study a single

batch of uncoated pellets was used throughout, although *in-vitro* release profiles shown in section 2.3 confirm reproducibility of the manufacturing process used in uncoated pellet manufacture. The success of the film coating procedure and the quality of the resulting film have been assessed qualitatively by microphotography and scanning electron microscopy and quantitatively by *in-vitro* dissolution testing. Microphotographs of uncoated pellets and pellets coated with the three polymer systems described previously, demonstrate the uniform smooth surface appearance exhibited by these multiparticulates (Figures 3.1 to 3.3).

Scanning electron micrographs of the surface of pellets coated with polymethacrylate, ethylcellulose and Silicone Elastomer polymers are presented in Chapter 4 (Figures 4.25 to 4.30). All qualitative evidence presented illustrates the smooth surface characteristics exhibited by these coated multiparticulates.

Figure 3.1. Microphotograph of uncoated pellets containing ibuprofen 70%w/w in Avicel PH101 (magnification x40).

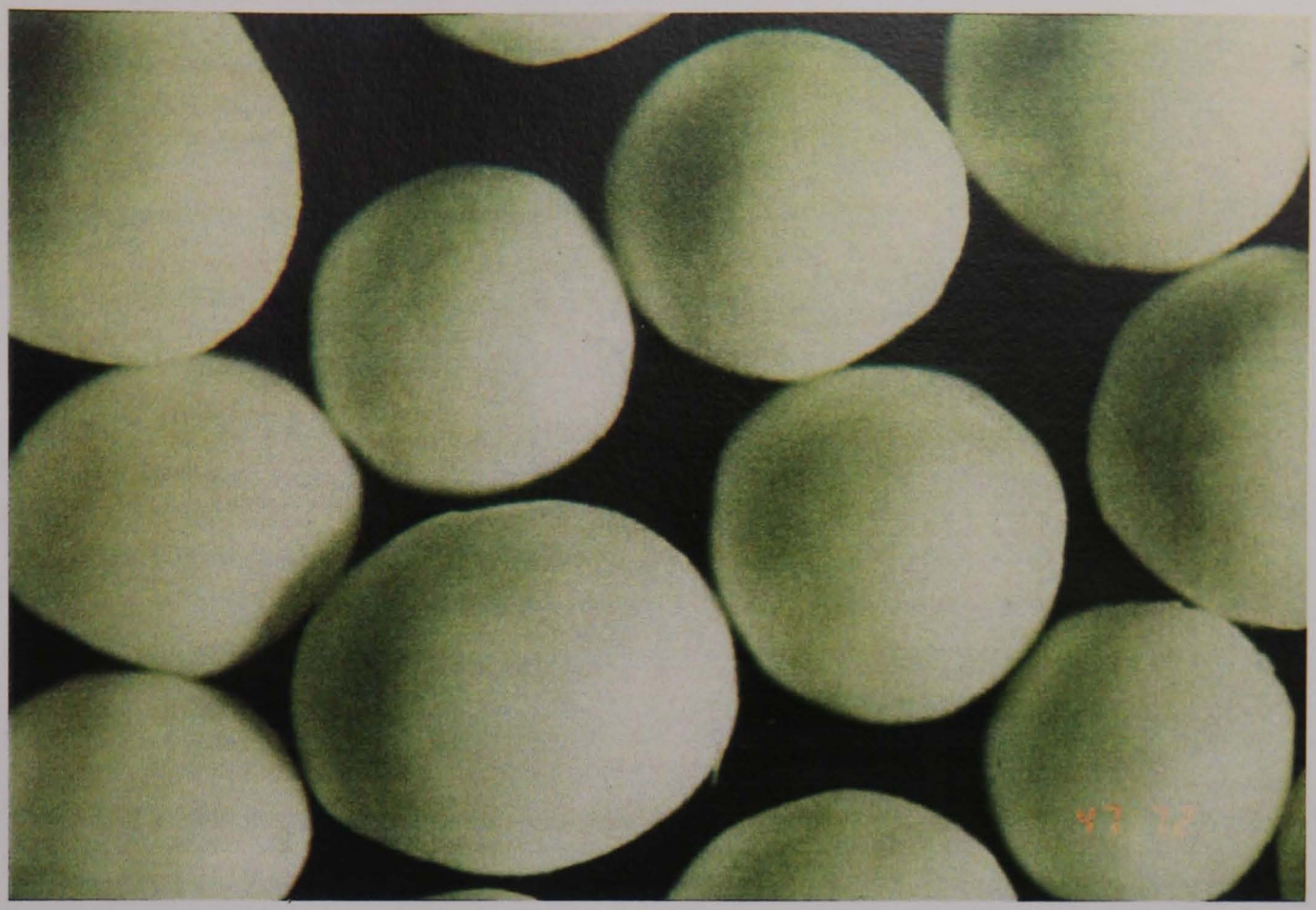


Figure 3.2. Microphotograph of ibuprofen pellets coated with the polymethacrylate dispersion (magnification x40).

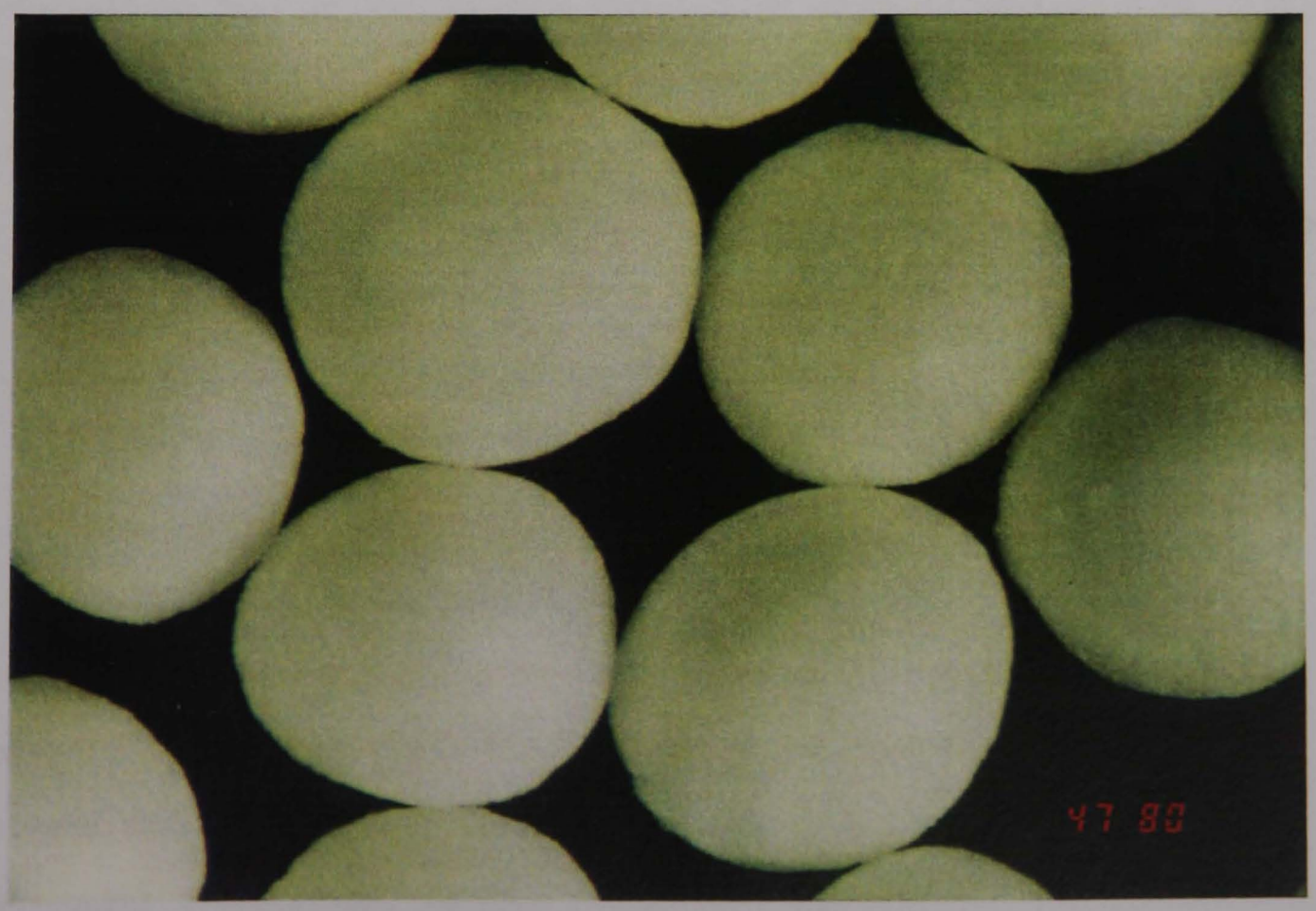


Figure 3.3. Microphotograph of ibuprofen pellets coated with Surelease (magnification x40).

Comparison of the *in-vitro* release profiles of coated pellets subjected to the post-coating "curing" stage with the control samples described in section 3.2, confirms that polymer coalescence and complete film formation is achieved whilst the pellets are in the stainless steel coating chamber. This is apparent as a consequence of the negligible difference in the release profiles of the control samples and pellets subjected to a post-coating drying stage, consisting of 24 hours storage at 40°C in a hot air oven (Figures 4.8, 4.10, 4.12, 4.13, 4.14, 4.15 and 4.16).

A study of the tensile properties of polymeric films as free-films is made subsequently in Chapter 5 and consideration is given to the effect of the formulation variables on the quality of the resulting film.

Chapter 3 is a precursor to Chapters 4 and 5 which consider the *in-vitro* drug release from uncoated and polymer coated pellets and the tensile properties of free-films and respectively. Both of these chapters involve a study of the three polymer systems, with the aim of ascertaining that polymeric film formulation which is best able to sustain the effect of the applied load associated with the compaction of coated pellets into tablets. A study is made of the tensile properties of polymeric films including elasticity, elastic compliance and Newtonian Viscosity and of the effect of polymer loading on the *in-vitro* release rates and the mechanism controlling drug release.

3.4. Conclusions.

The film coating of multiparticulates using aqueous polymeric dispersions requires uniform application of polymer in a closely controlled drying environment. An equilibrium must be established between the rate of application of liquid to the fluidised bed and its subsequent evaporation, polymer coalescence and complete film formation.

A major role of plasticiser in aqueous polymeric dispersion film coating operations is one of facilitating a reduction in the minimum film forming temperature (MFT) of the polymer to below the equilibrium temperature of the coating chamber. This is in addition to its influence on the elasticity and permeability of the resultant film.

The success of the film coating operation may be qualitatively assessed by microphotography and scanning electron microscopy and quantitatively assessed by *in-vitro* dissolution testing. It is important with the application of any aqueous polymeric dispersion to ensure that polymer coalescence and complete film formation is achieved during the coating process. This may be confirmed by there being negligible difference in the *in-vitro* release profiles of coated pellets subjected to a post-coating drying operation or so-called "curing" stage and those which are not.

CHAPTER 4

IN-VITRO DRUG RELEASE STUDIES FROM UNCOATED AND COATED PELLETS CONTAINING IBUPROFEN

4.1. Introduction.

Dissolution is defined as the process in which a solid substance enters into the solvent phase yielding a solution; fundamentally it is controlled by the relative affinity of the solute molecules between the solid and the solvent. On oral administration pharmaceutical dosage forms undergo dissolution in biological media, followed by absorption of the drug into the systemic circulation. In determining the dissolution rate of drugs from solid dosage forms under standardised conditions, it is necessary to consider several physicochemical processes in addition to the processes involved in the dissolution of pure chemical substances. Factors which may influence the dissolution characteristics of drugs include the physical characteristics of the dosage form, the wettability of the dosage unit, the penetration ability of the dissolution medium and any swelling, disintegration or deaggregation of the dosage form.

For drug-containing pellets which are surrounded by a release-retarding polymeric membrane, the process of dissolution may broadly be illustrated by Figure 4.1.

4.1.1. Theory of Dissolution.

For dissolution of a solid to occur, solute molecules must first escape from the surface of the solid and then undergo some form of transport process away from the surface into the bulk solution. Depending upon the relative significance of these two processes and the means by which the transport is effected, it is possible to set up physical models to account for the resulting dissolution behaviour. For the dissolution of pure substances, three models have been proposed, either individually or in combination to describe dissolution-rate mechanisms (Swarbrick, 1992).

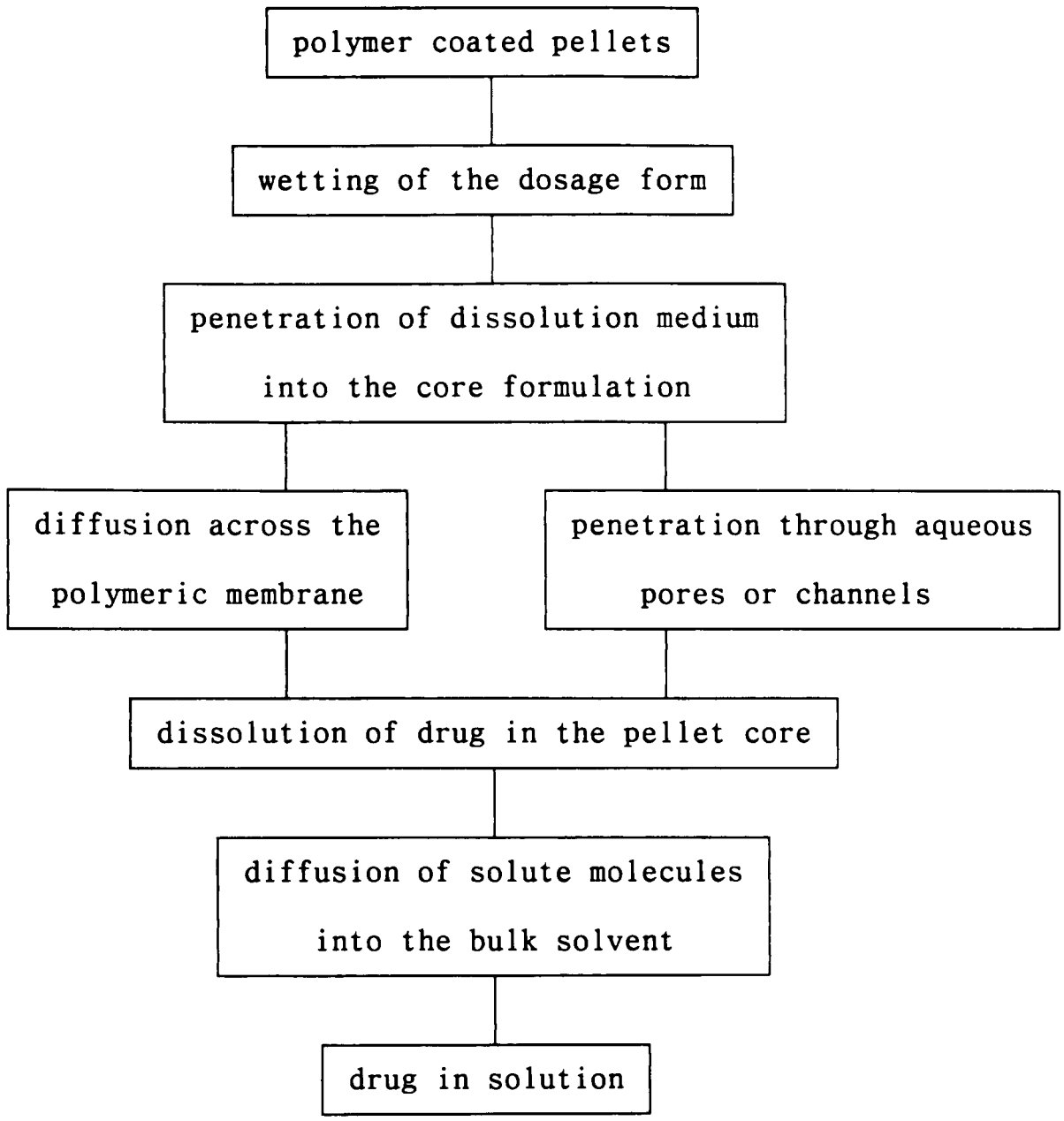


Figure 4.1. Schematic illustration of the process of *in-vitro* dissolution of drug from non-eroding pellets of spherical geometry surrounded by an aqueous insoluble polymeric membrane.

4.1.1.1. Diffusion Layer Model.

Probably initially proposed by Nernst and Brunner in 1904, this model assumes a static liquid film exists adjacent to the solid surface of thickness *l*, a negative velocity component in the direction perpendicular to the surface. The reaction at the solid-liquid film interface is assumed to be rapid. Once the molecules pass the liquid film-bulk film interface, rapid mixing occurs and the concentration

gradient is destroyed. The rate of the solute movement and therefore the dissolution rate are determined entirely by Brownian motion diffusion of the molecules in the liquid film (Figure 4.2).

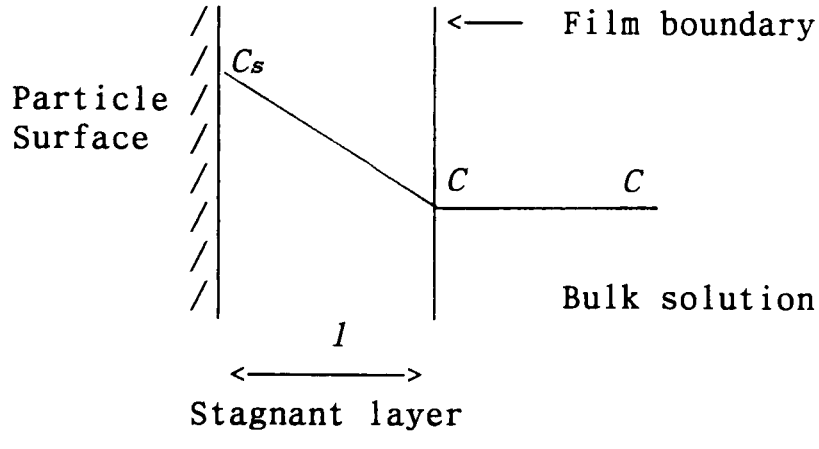


Figure 4.2. Schematic illustration of the diffusion layer model.

4.1.1.2. Interfacial Barrier Model.

This model assumes that the reaction at the solid surface and therefore the diffusion across the interface is not significantly slower than diffusion across the liquid film. As a consequence solid-solution equilibrium may not be assumed; this must be accounted for in the model. The process at the solid-liquid interface is rate limiting in respect of the transport process. This model is illustrated in Figure 4.3 where the relatively rapid transport process now occurs by diffusion through a static liquid film.

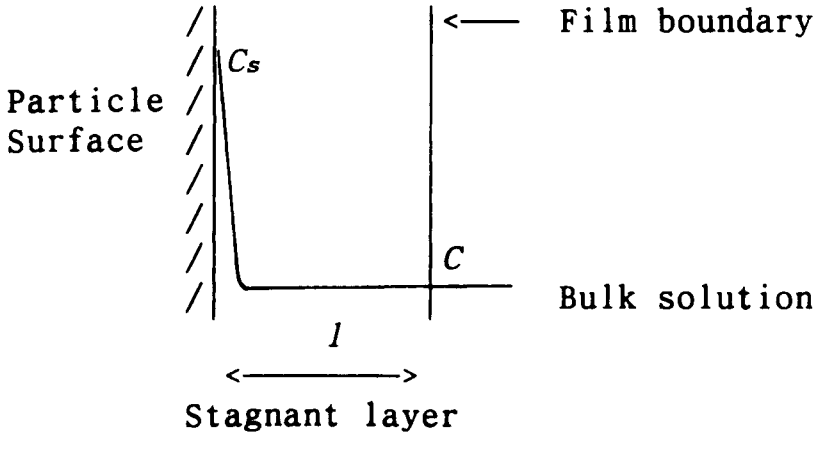


Figure 4.3. Schematic illustration of the interfacial layer model.

4.1.1.3. Danckwert's Model.

This model (Figure 4.4) assumes that transport of solute away from the solid surface is achieved by macroscopic packets of solvent reaching the solid-liquid interface by eddy diffusion in a random fashion. These solvent packets attach themselves to the surface. During their residence at the interface, these packets are able to absorb solute and are then replaced by diffusional motion, by fresh packets of solvent. Assuming that the solid surface reaction is instantaneous, this surface renewal process may then be related to the solute transport rate and hence dissolution.

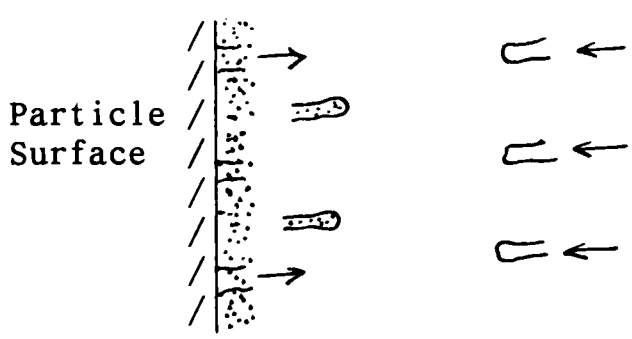


Figure 4.4. Schematic illustration of Danckwert's model.

4.1.2. Film Theory of Dissolution.

The film theory of dissolution is based on the assumption that the surface of the dosage form in contact with the dissolution medium does not change during the process of dissolution and that the dissolution medium is stagnant.

Under these simplified conditions Noyes and Whitney describe the quantitative kinetics of dissolution of a substance from an even surface by the movement of molecules at the solid-liquid interface and diffusion of dissolved molecules in the dissolution medium. Equation 4.1 describes this theory:

$$\frac{dc}{dt} = K\,(C_s - C) \qquad \text{Equation 4.1.}$$

where dc/dt is the change in concentration as a function of time, K is the dissolution rate constant, C_s is the solubility or saturation concentration and C is the solution concentration at time t.

As a consequence of the motionless nature of the liquid, a saturated solution is formed at the solid-liquid interface and the concentration decreases with growing distance from the interface reaching a finite concentration C' in the surrounding liquid. The layer of saturated solution functions as the diffusion barrier layer. Consequently according to Fick's Law of Diffusion, the dissolution rate constant K, is directly proportional to the coefficient of diffusion D. Hence $K = D/Vl$ where V is the solution volume and l is the thickness of the diffusion layer.

Since the rate of diffusion is proportional to the surface area of the dissolving substance S, employing the assumption of Noyes and Whitney, Nernst and Brunner, modified Equation 4.1 to incorporate the diffusion coefficient and the surface area of the dissolving substance:

$$\frac{dc}{dt} = \frac{DS}{Vl}(Cs - C') \qquad \text{Equation 4.2.}$$

The dissolved substance moves according to differences in the concentration gradient between the layer that is in direct contact with the solid surface and the other layers of the medium, provided that there is now accelerated movement of the medium. If the liquid surrounding the dissolving substance is set in motion by either laminar or turbulent flow, the dissolved molecules will move more quickly into the ambient liquid. In such instances the resultant solution is homogeneously mixed at all times. In the case of sparingly soluble substances, C' is very low in the surrounding medium and Equation 4.2 simplifies to the following:

$$\frac{dc}{dt} = KSC_s \qquad \text{Equation 4.3.}$$

Nernst proposed this film theory in 1904 and it demonstrates some of the basic principles concerning the dissolution of single particulate systems. When a solid particle is immersed in an agitated liquid and allowed to dissolve, the bulk liquid will continuously be exposed to the solid surface with a certain velocity. At any given instant during the process of solubilisation or dissolution, a stagnant layer or film surrounds the particle. This stagnant layer of thickness *l* and termed the *Nernst-Brunner thickness layer*, is not necessarily hydrodynamically stagnant although it behaves as such and a concentration gradient exists within it (Figure 4.2). C_s represents the concentration at the surface or the saturation concentration and C is concentration at the boundary between the bulk solution and the film. It is assumed that the thickness of this boundary layer is independent of the particle size. Assuming steady state exists, Fick's first law of diffusion may be employed:

$$J = - D \frac{\delta C}{\delta x} \qquad \text{Equation 4.4.}$$

where the previous notation applies. $\delta C/\delta x$ is the concentration gradient and may be considered constant by virtue of it being the slope of the line (Figure 4.2).

4.1.3. The importance of sink conditions.

In the design of a reliable *in-vitro* dissolution test model which is allegedly capable of mimicking the dissolution process *in-vivo*, it is essential that the model simulates as far as possible, prevailing conditions within the biological system. One such condition is the

maintenance of nearly perfect sink conditions during *in-vitro* dissolution rate determinations. The drug concentration within the dissolution medium must not exceed 10 to 20% of its solubility (Swarbrick, 1992). This condition is essential since during a dissolution-rate absorption process, there is no significant drug concentration build-up in the gastro-intestinal fluids; they act as an infinite sink.

4.1.4. Forced convection dissolution devices.

The systems widely used for *in-vitro* dissolution testing with the provision of such conditions are fixed fluid volume, multiple phase and continuous fluid flow devices.

4.1.4.1. Fixed fluid volume.

Dissolution studies are undertaken as the phrase suggests, under conditions of fixed and finite aqueous dissolution fluid volume. The volume is such that the solute drug concentration is less than 10 to 20% of the drug solubility throughout the entire test. This test method is unsuitable for both sparingly soluble or exceptionally high dose drugs, due to the practical limitations associated with the large fluid volume which would be necessary for the maintenance of sink conditions.

4.1.4.2. Multiple phase systems.

Here drug is dissoluted in an aqueous medium, but it is then either partitioned off into a water-immiscible organic phase or adsorbed onto a solid. Sink conditions are provided by the removal of solute molecules throughout testing.

4.1.4.3. Continuous fluid flow.

This method provides a relatively simple and convenient system and it is suitable for the determination of dissolution rates for all drugs

irrespective of their solubility and potency. Sink conditions are maintained by the constant removal of the dissolved drug from the dissolution medium. This is achieved by the continuous elimination of the filtered dissolution medium from the dissolution chamber and the simultaneous addition of fresh solvent to the vessel.

4.1.5. Membrane-controlled drug release.

The drug release mechanism from a membrane modified drug delivery system, in which the membrane ultimately controls the drug release characteristics of the dosage form, is essentially based on the principles of diffusion. Solid drug in the core of a membrane coated pellet must undergo dissolution within the core prior to delivery of solute molecules into the donor compartment. This process is facilitated largely by diffusional transport of solute molecules across the polymeric membrane.

According to Fickian diffusion principles, the rate of drug release dQ/dt at steady state is given by

$$\frac{dQ}{dt} = DA\frac{C_{md} - C_{mr}}{l} = DA\frac{K_d C_d - K_r C_r}{l} \qquad \text{Equation 4.5.}$$

where C_{md} and C_{mr} are the membrane drug concentrations at the delivery and receptor side respectively and where D is the coefficient of diffusion through the membrane, A is the membrane area, C_d the drug concentration in the delivery compartment, C_r the drug concentration in the receptor compartment, and K_d and K_r represent the partition coefficients between the membrane of drug in delivery and receptor solutions respectively.

Under sink conditions $C_r << C_d$ in the delivery compartment therefore

$$\frac{dQ}{dt} = \frac{DAK_d}{l} C_d = \frac{PAC_d}{l} \qquad \text{Equation 4.6.}$$

where $P = K_d D$, which represents the permeability behaviour of the drug from such a system.

The drug in the delivery compartment is in the form of a suspension. Therefore, the concentration of the resulting solution has a constant value, since the amount of drug lost due to permeation into the receiving compartment is replaced by drug from the core in solid form, thus yielding drug release which may be described by zero order kinetics. Equation 4.7 describes such behaviour; the right hand side of the equation remains constant

$$\frac{dQ}{dt} = \frac{PAC_s}{l} \qquad \text{Equation 4.7.}$$

C_s represents the drug solubility in the delivery compartment solution.

According to Fick's law, the rate of drug release dQ/dt, depends on the coefficient of diffusion of drug through the coating D_m, coating area A and the thickness of the coat l; partition coefficient of the coating/water K; and the concentration of the saturated solution C_s. These parameters are expressed collectively in Equation 4.8:

$$\frac{dQ}{dt} = \frac{D_m A K (C_s - C)}{l} \qquad \text{Equation 4.8.}$$

Under sink conditions and integrating, Equation 4.8 becomes

$$Q = KAC_s t = \frac{PAC_s}{l} t \qquad \text{Equation 4.9.}$$

where K and P represent the diffusion rate and penetration rate constants respectively.

Lippold et al. (1990) however reports that drug release from coated tablets is more complex than this. Lipid coating is practically impermeable to hydrophilic molecules and weakly permeable to water but permeable only to undissociated lipophilic molecules. This inhibits the formation of a saturated drug solution within the core formulation. These are porous membranes permeable to both hydrophilic/lipophilic molecules and water.

4.1.6. Interpretation of dissolution data.

The *in-vitro* dissolution data obtained for modified-release dosage forms may be expressed in many ways but expression of cumulative amount of drug released Q expressed as a function of time, is as an informative method as any in the elucidation of the drug release mechanism. These functions can further be expressed graphically, and fall into four basic categories (Figure 4.5).

For a dosage form in which the amount of drug permeating to the solution is constant for each time interval, $Q = kt$ can express this process. Figure 4.5a represents dissolution displaying zero-order kinetics. This type of drug release is characteristic of sustained- or controlled-release dosage forms.

Figure 4.5b illustrates dissolution kinetics from a dosage form exhibiting first-order kinetics, explained by the equation $Q = 1 - kt$. Most conventional dosage forms exhibit this dissolution mechanism, including some modified-release preparations. Some specialised dosage forms contain many drug particles of the same size and shape or their agglomerates that dissolve evenly. In such cases the dissolution process can be explained by the cube-root law, where $Q = 1 - (1 - kt)^3$ (Figure 4.5c).

For a matrix drug delivery system where drug dissolves from the matrix, by dissolving in the matrix-forming substance, the process is

controlled by diffusion. The diffusion-controlled dissolution process can be expressed by the square-root equation, where $Q = k\sqrt{t}$; this process is expressed by Figure 4.5d.

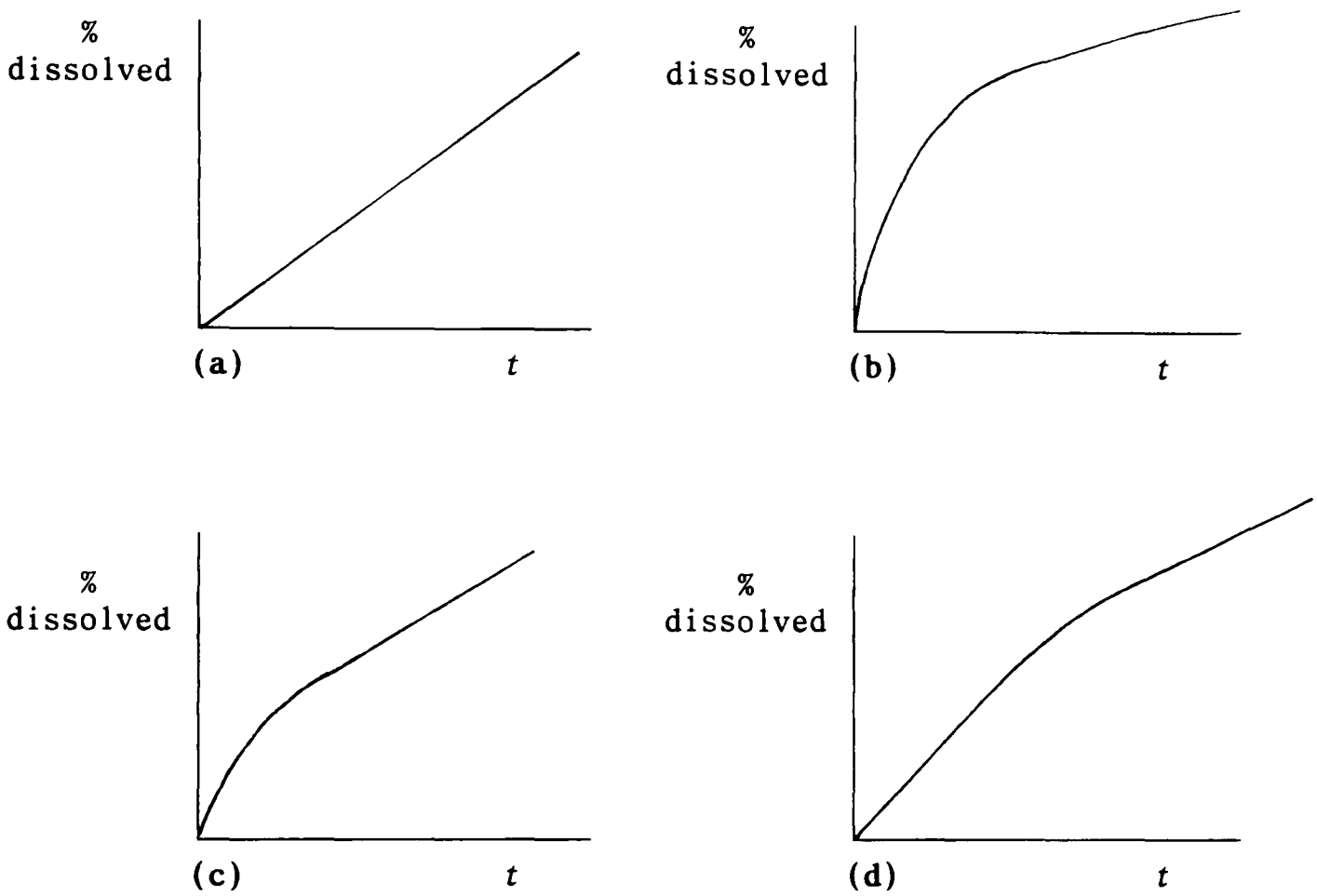


Figure 4.5. Graphical interpretation of dissolution profiles in terms of cumulative % drug dissolved, as a function of time: (a) zero-order process; (b) first-order process; (c) dissolution adhering to cube-root law; (d) dissolution adhering to square-root Equation.

It is important to emphasise that the dissolution kinetics of a given dosage form may not unequivocally fit into one of the above categories. Complex dissolution profiles may result, feasibly representing a combination of two or more of the release mechanisms discussed.

4.2. Methodology.

4.2.1. Apparatus.

In-vitro dissolution testing was performed in standard USP XXII, type II (paddle) apparatus containing 900ml of pH 6.8 phosphate buffer (BP formula), maintained at 37°C with a paddle rotation speed of 100rpm. Samples were analysed in one of the following ways; testing was performed using both systems to ensure that the two methods gave reproducible results. Sink conditions were maintained throughout *in-vitro* testing.

The first system consisted of a six station flow-through dissolution apparatus attached to a CECIL CE595 Double Beam Digital u.v. spectrophotometer. Matched 10mm flow-through cells were used and samples were analysed for ibuprofen at 264nm. The concentration of ibuprofen present in a given sample is expressed as a percentage of the initial strength of the dosage form (following calibration with a blank and 100% standard). Each dissolution test was performed using six vessels and the mean per cent of drug released at any one time was computed. Results are expressed graphically in most cases excepting those situations where greater clarity is achieved when data is tabulated.

The second apparatus consisted of three six station dissolution tanks and a Hewlett Packard 8450A Diode Array spectrophotometer. Samples were removed at specified time intervals and lost-volume due to sample removal was compensated for by calculation, as shown subsequently. This system measures spectra over a specified wavelength range; it is claimed that greater accuracy is achieved with this multiwavelength method. In this work a range of 245-300nm was used and measured spectra were compared to a measured standard, details of which were retained in the memory of the software. As assayed samples were not returned to the dissolution vessels after measurement, the volume remaining in each vessel was reduced by the 6ml sample volume after each sample was removed. A correction routine was used which allowed for this reduction

in the dissolution volume and also the amount of solute dissolved in the removed sample. The correction formula is as follows:

$$D_c = D\,[V - (n-1)\,V_s]/V + (D_s)_{n-1}$$

where D_c = % dissolved corrected for lost volume

D = % dissolved computed from absorbance value

V = initial volume of dissolution medium

V_s = sample volume

n = total number of samples taken including the current sample

$(D_s)_{n-1}$ = amount of dissolved solute lost in all previous samples

The amount of dissolved solute lost in all samples including the current one is

$$(D)n = (D_s)_{(n-1)} + D(V_s/V)$$

$(D)n$ becomes the $(D_s)_{(n-1)}$ for the next sample. The initial volume is 900ml and the sample volume V_s = 6.0ml.

4.2.2. Compliance of ibuprofen with the Beer-Lambert Equation.

The u.v. and visible spectra of organic compounds are associated with transitions between electronic energy levels. Excitation of electrons above 200nm from p- and d-orbitals, and π-orbitals and π-conjugated systems, gives rise to informative spectra which is easily measured.

The energy of electronic excitation is related to wavelength by the following:

$$E\ (kJ/mol) = 1.19 \times 10^5 / \lambda\ (nm).$$

Therefore at 264nm ($\lambda_{max.}$ ibuprofen) the energy of electronic excitation is 451kJ.

Two empirical laws have been formulated about the absorption intensity. Lambert's Law states that the fraction of incident light absorbed is independent of the intensity of the source. *Beer's Law* states that the absorption is proportional to the number of absorbing molecules.

The Beer-Lambert Equation is therefore as follows:

$$\log_{10} (I_0/I) = \epsilon c l = A$$

where I_0 and I are the intensities of the incident and transmitted light, ϵ is the molar extinction coefficient ($dm^3\ mol^{-1}\ cm^{-1}$), c is the concentration ($mol\ dm^{-3}$), and l is the length of the light path or path length and A is the absorbance. The factor log (I_0/I) is therefore proportional to the amount of absorbing material present in the sample, providing the amount of absorbing material present in the sample is not modified by a molecular reaction. The excitation energy at 264nm is sufficient to initiate such a reaction should the sample be left in the u.v. beam for longer than is necessary.

The absorbance, also known as the optical density is related to transmittance (T) as follows:

$$A = 1/T = \epsilon c l$$

Since ϵ and l are constant, a linear relationship between absorbance and concentration of drug, indicates compliance of that compound with the Beer-Lambert Law.

Figure 4.6 is a Beer-Lambert plot for ibuprofen in pH 6.8 phosphate buffer at 264nm. Readings were made in triplicate and the mean values

are as plotted. In order to ascertain the wavelength at which the excitation of molecules was maximum, a scan was performed over a wavelength range of 300-220nm. The $\lambda_{max.}$ was determined to be 264nm. This is in accordance with the BP value for ibuprofen.

4.2.3. Interference of inactive excipients.

In order to ascertain the effect of the presence of excipients other than ibuprofen, on the absorption spectra of this compound in pH 6.8 phosphate buffer and at 264nm, standard solutions were prepared equivalent to 800mg/900ml (888mg/1000ml) ibuprofen.

It was necessary for each film coating formulation to consider the effect of the film coating excipients on the absorption spectra. By crushing coated pellets and sonicating for one hour in the buffer solution, the drug dissolves and a simple filtration process enables the sample to be spectrophotometrically assayed.

The following standards were prepared, each in pH 6.8 phosphate buffer:

i) 888mg/1000ml ibuprofen pure drug

ii) equivalent of 888mg/1000ml ibuprofen presented as crushed pellets coated with Surelease dispersion; (uncoated pellets containing 80%w/w drug, expressed as per cent weight dry solids).

iii) equivalent of 888mg/1000ml ibuprofen presented as crushed pellets coated with Silicone Elastomer; (uncoated pellets containing 80%w/w drug, expressed as per cent weight dry solids).

iv) equivalent of 888mg/1000ml ibuprofen presented as crushed pellets coated with Eudragit RS/RL30D; (uncoated pellets containing 80%w/w drug, expressed as per cent weight dry solids).

Using a pestle and mortar, coated pellets were ground to powder; the required quantity was weighed into an analytical weighing boat using a five figure Mettler analytical balance.

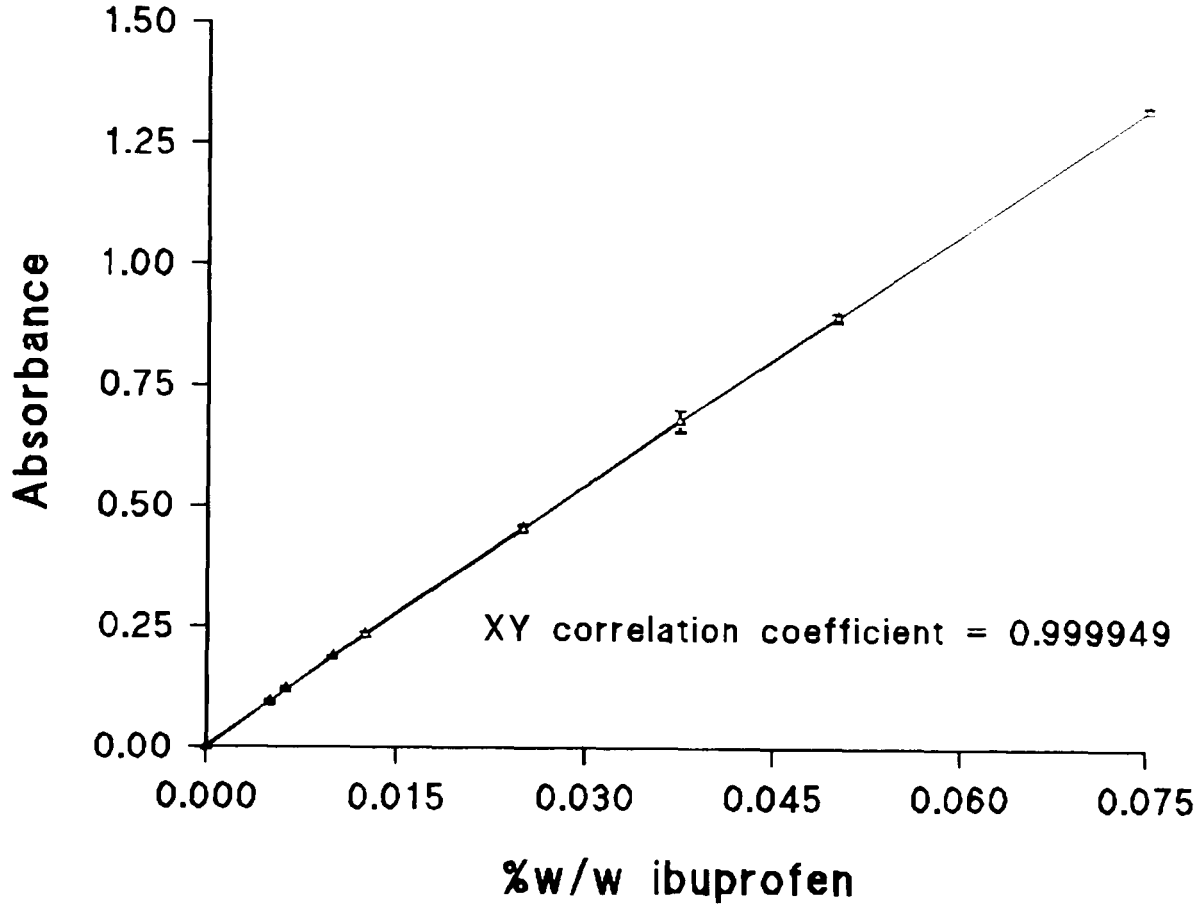


Figure 4.6. Beer-Lambert plot for ibuprofen in pH 6.8 phosphate buffer BP at 264nm.

The powder was transferred to a volumetric flask, the washings added and the standard made to volume with buffer. Each standard was sonicated for a period of one hour such that the ibuprofen was completely in solution. Samples were withdrawn from each flask, filtered to remove the insoluble component and scanned over a wavelength range of 300-220nm using a calibrated Perkin Elmer 554 spectrophotometer.

For each test sample, the peak height and the peak wavelength were identical to that of the standard solution containing 888mg ibuprofen in 1000ml of buffer. Also for each sample, a replicate scan was performed

and the resulting traces indicated no interference by other excipients, with the spectra of ibuprofen within this wavelength range. It was concluded therefore that u.v. spectroscopy at 264nm was a suitable analytical technique for monitoring the *in-vitro* release of ibuprofen.

4.3. Results and Discussion.

Three uncoated pellet formulations containing ibuprofen 60%w/w, 70%w/w and 80%w/w with Avicel PH101 were coated with aqueous polymeric release retarding membranes. For each coating study, one batch of uncoated pellets was used throughout, although release profiles shown previously indicate favourable reproducibility of drug release by replicating the manufacturing process for uncoated product.

4.3.1. Drug release from uncoated pellets.

The incorporation of ibuprofen in a pellet formulation containing microcrystalline cellulose (Avicel PH101), results in the formation of multiparticulates which are essentially spherical solid matrices. Drug removal from these uncoated entities by *in-vitro* dissolution of pellets containing ibuprofen and Avicel PH101, yields visibly intact spheres from which the drug has been leached; microcrystalline cellulose as a consequence of being water insoluble and present in quantities as low as 20%w/w dry solids, is able to maintain the spherical shape of these pellets following drug removal by *in-vitro* dissolution testing. Dissolution kinetics from uncoated pellets comprising drug mixed with an insoluble excipient, in this case microcrystalline cellulose, may be considered as drug release from homogeneous matrices.

It is possible to consider drug release from an homogeneous matrix from a simple planar surface involving unidirectional leaching and extraction, corresponding closely to the release process from an insoluble matrix, either in the form of a tablet or as uncoated pellets.

The mechanisms of release from these systems can be treated in two ways, firstly by extraction of the drug by a simple diffusional process through the homogeneous matrix and secondly leaching of drug by the solvent phase, which is able to enter the drug-matrix phase through pores, cracks and intragranular spaces. In the former case, drug presumably partitions from the crystal surfaces into the uniform matrix and out into the bathing solvent, which acts as a perfect sink. In the latter case however, drug dissolves slowly in the permeating fluid phase and diffuses from the system along the cracks and capillary channels filled with the extracting dissolution medium. Swarbrick (1992) comments that in most cases it is accepted that intragranular diffusion is minimal.

Complication of the above theories arises as a consequence of the occurrence of one or more of the following situations arising; (a) partial dissolution of matrix substances; (b) simultaneous breakup of the matrix; (c) drug on the surface of the matrix being released more rapidly than drug in the matrix and (d) one fraction of the dose being in a different, non-matrix, readily available form.

4.3.1.1. Drug release from a homogeneous matrix of planar geometry.

Assuming that the matrix does not dissolve and that the drug is uniformly distributed in it, drug release from this matrix surface under perfect sink conditions is described by

$$Q = [DtCs(2W - Cs)]^{1/2} \qquad \text{Equation 4.10.}$$

where Q is the amount of drug released after time t per unit exposed area; D is the coefficient of diffusion of the drug in the homogeneous matrix media; W is the total amount of drug present in the matrix per unit volume and C_s is the solubility of the drug in the matrix substance.

In summary, Equation 4.10 may be rewritten as

$$Q = f(\sqrt{t}) \qquad \text{Equation 4.11.}$$

indicating that drug release is dependent on the square root of time. This equation is known as the $\sqrt{t}$ Equation.

4.3.1.2. Drug release from a granular matrix of planar geometry.

The dissolution and release of drug from a granular matrix system under perfect sink conditions, for the leaching type of release mechanism occurring through diffusion movement within intergranular openings, can be expressed as

$$Q = \left[\frac{D\epsilon}{\tau} (2W - \epsilon C_s) C_s t \right]^{1/2} \qquad \text{Equation 4.12.}$$

where τ is the tortuosity factor of the capillary system and ϵ is the porosity of the matrix (Swarbrick, 1992). This expression is based on the existence of a pseudo-steady-state condition during the release process and on the assumption that the drug particles are quite small relative to the average distance of diffusion and are uniformly distributed in the matrix. Providing $W > C_s$ or ϵC_s by a factor of 3 to 4, then Equation 4.12 can satisfactorily define the release of drug from such a system. If the situation were apparent that $W < C_s$ or ϵC_s, then a different expression would apply since drug would no longer be present as a solid.

As drug is released, the porosity of the matrix increases in accordance with the volume of the drug. This difference in porosity would correspond directly to the volume of free space previously occupied by the extracted component(s).

Hence

$$\epsilon = \epsilon_0 + VW \qquad \text{Equation 4.13.}$$

where ϵ_0 and ϵ represent initial and final porosities respectively, of the matrix. If the amount of drug per unit volume of matrix is W, then the specific volume of the drug V, will be inversely proportional to the density of the drug, since V = 1/density. When the initial porosity ϵ_0 is very small or when the drug has a large volume compared with the volume of the matrix, the porosity at any subsequent time ϵ, approximates the product of V and W. Hence Equation 4.12 may be modified:

$$Q = W \left[\frac{DV}{\tau} (2 - VC_s) C_s t \right]^{1/2} \qquad \text{Equation 4.14.}$$

This equation implies that the fraction of drug released at any given time is essentially independent of the total amount of drug in the matrix, W.

4.3.2. Drug release from polymer coated pellets.

Ozturk et al. (1990) reported that drug release from pellets coated with ethylcellulose may occur by several mechanisms, including solute diffusion through the continuous polymeric membrane, through plasticiser channels and/or through aqueous pores; the solute molecules being driven by the difference in osmotic pressure between solute within the core of a pellet and that in the dissolution medium. Ozturk also considered the effect of the presence of cracks within the film coat on drug release. The author confirms the presence of plasticiser being of paramount importance in forming a continuous film, however that diffusion of drug through plasticiser channels is unlikely to make a significant contribution to the overall drug release rate. Ozturk concluded that

drug release from pellets coated with an ethylcellulose pseudolatex is attributable to both diffusion of solute molecules and also as a function of the relative osmotic pressure of the medium.

Ozturk et al. (1990) and Zhang et al. (1991) both indicate that the mechanism controlling drug release is influenced by the thickness of the applied coating. Figures 4.7, 4.9, 4.11, 4.14 and 4.15 all show that drug release is retarded simultaneously with increasing polymer loading, indicating that the film is controlling the release process. Zhang et al. define the critical coating level (CCL) as being that coating level at which the drug release mechanism becomes completely barrier controlled. These authors found that the drug release rate and the drug release mechanisms were dependent upon the coating level. At low coating levels the pore control mechanism predominates, while at higher coating levels drug release is mainly membrane or barrier controlled. This is supported by Figures 4.7, 4.9 and 4.11, in that at zero or low polymer loading, the drug release rate cannot be described as being time independent; it is very much time dependent. However at higher coating levels corresponding to an increasing membrane thickness (above the so-called CCL), the drug release profile is exhibiting zero order kinetics (the rate of drug release is independent of time); the release profile of cumulative per cent ibuprofen released against time is linear.

At lower coating levels the membrane is relatively more porous and the drug takes the route of least resistance for release from the core of the individual multiparticulates.

Wouessidjewe et al. (1991) consider the effect of multiple film coverage in sustained release pellets. As the film is applied to individual pellets, a continuous membrane is formed by the building up of overlapping segments. Above the CCL, it may be concluded that all of the "holes" are covered and that a continuous and complete membrane is

enveloping each individual pellet. As a consequence of building a continuous film by spraying atomised dispersion one might expect that imperfections within the film coat are present. This is discussed in Chapter 5 in the study of free films, which are inherently less likely to contain imperfections than the membrane surrounding film coated pellets.

Wouessidjewe concludes that sprayed polymeric membranes leads to the formation of discrete films overlapping each other. Once the CCL is exceeded, it may be assumed that complete membrane formation has occurred.

As the coating thickness increases, fewer pores are available for drug transport thus retarding drug release. It is more likely that drug release is now occurring by diffusion across the polymeric membrane rather than by diffusion through pores or channels or imperfections within the film coat.

All coated and uncoated pellets studied remained intact during drug removal by *in-vitro* dissolution testing.

Figures 4.7, 4.9 and 4.11 show *in-vitro* release profiles for pellets coated with increasing levels of polymethacrylate containing aqueous dispersions; formulation details of which are given in Chapter 3. On the strength of preliminary feasibility coating studies, a desired polymer level was selected for each batch being studied, representing pellets containing 60%w/w, 70%w/w and 80%w/w ibuprofen (expressed as percentage dry solids present in the uncoated pellet formulation).

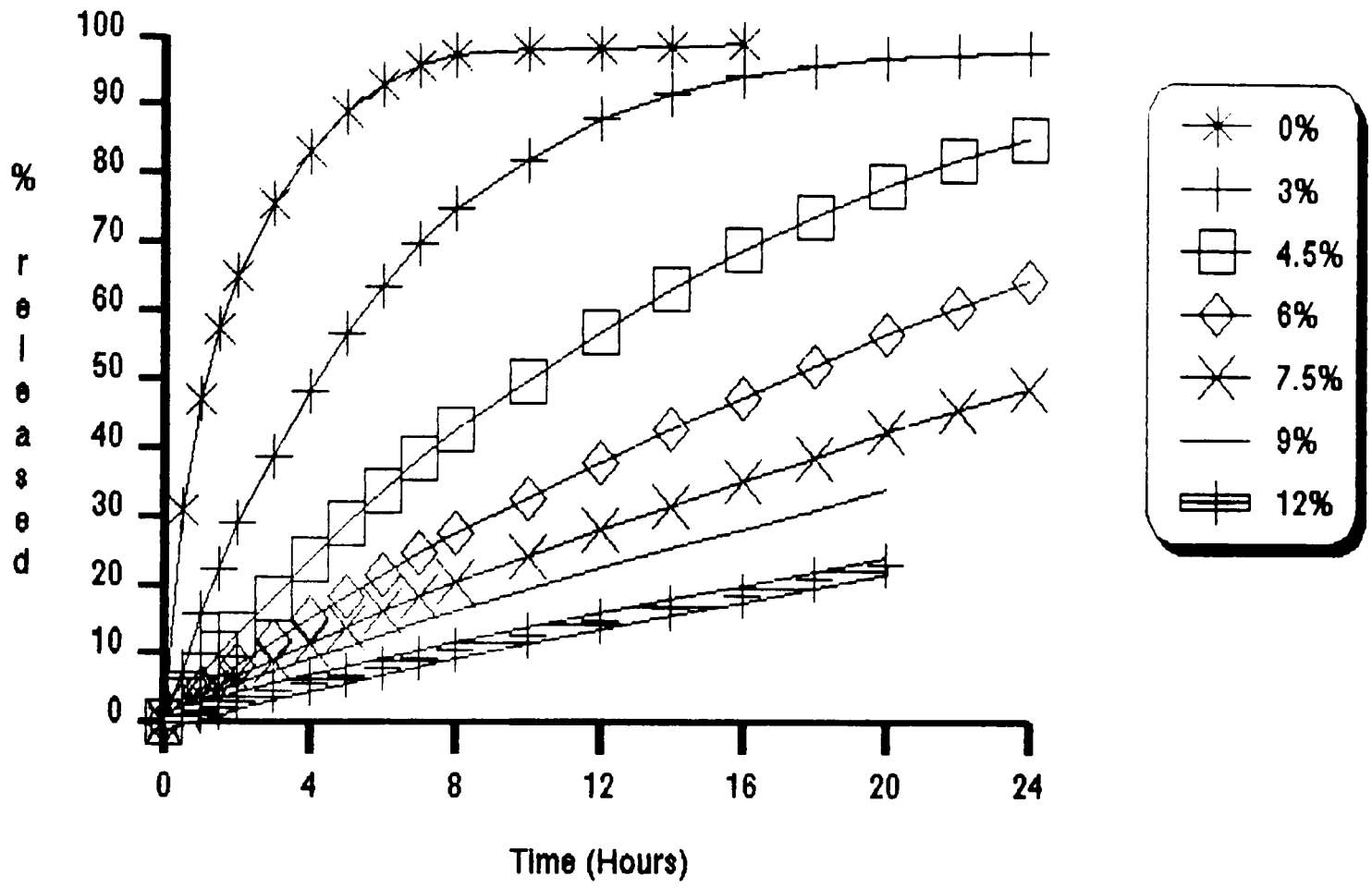


Figure 4.7. *In-vitro* drug release from 800mg of ibuprofen pellets containing 80%w/w ibuprofen (expressed as % weight dry solids in uncoated formulation) coated with an *x*% weight increase (see key), applied as an aqueous polymeric dispersion containing Eudragit RS/RL30D.

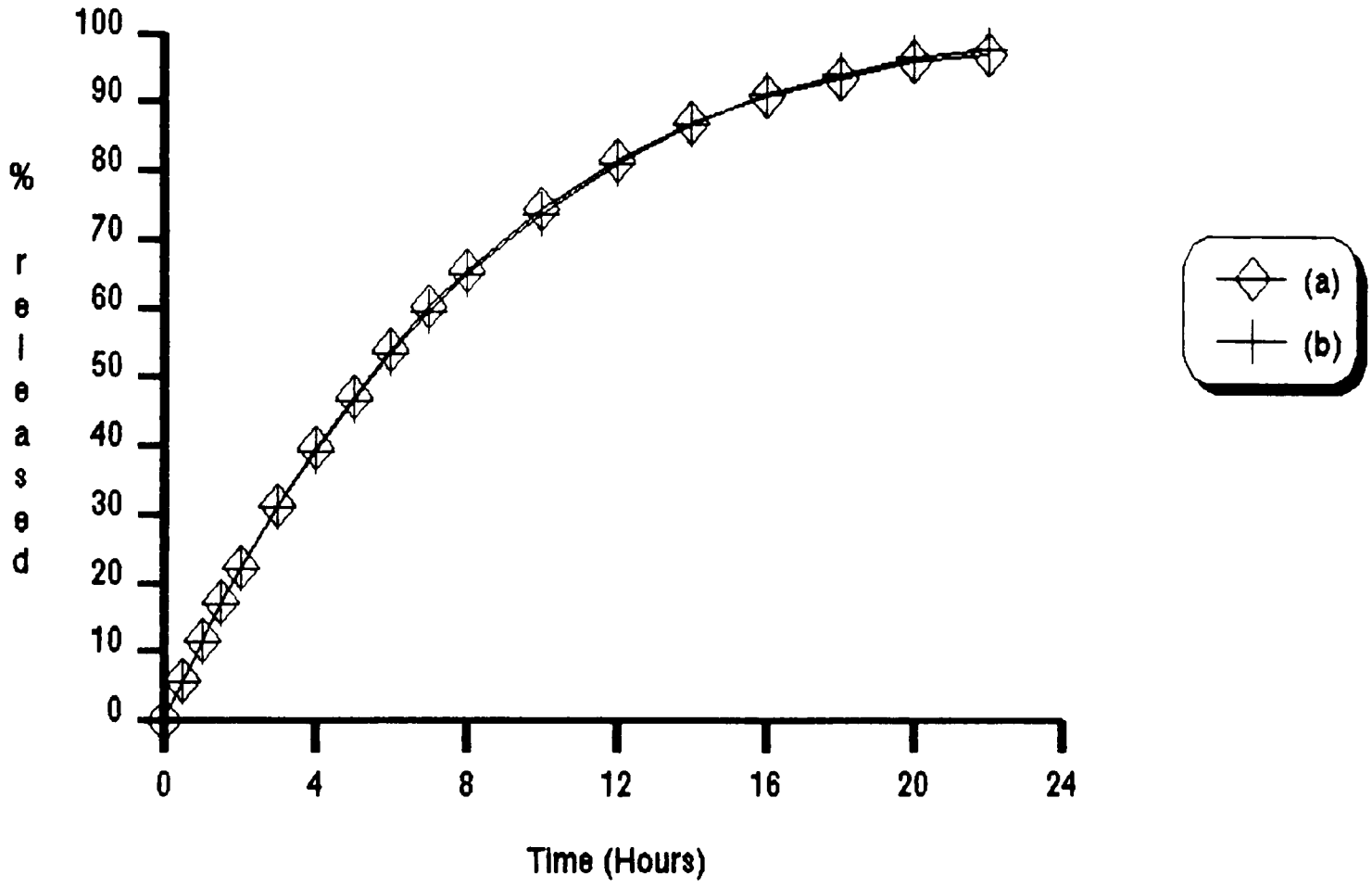


Figure 4.8. *In-vitro* drug release from 800mg of ibuprofen pellets containing 80%w/w ibuprofen (expressed as % weight dry solids in uncoated formulation) coated with a 4.5% weight increase, applied as an aqueous polymeric dispersion containing Eudragit RS/RL30D; (a) pellets subjected to a post-coating "curing" stage; (b) pellets not subjected to a post-coating "curing" stage.

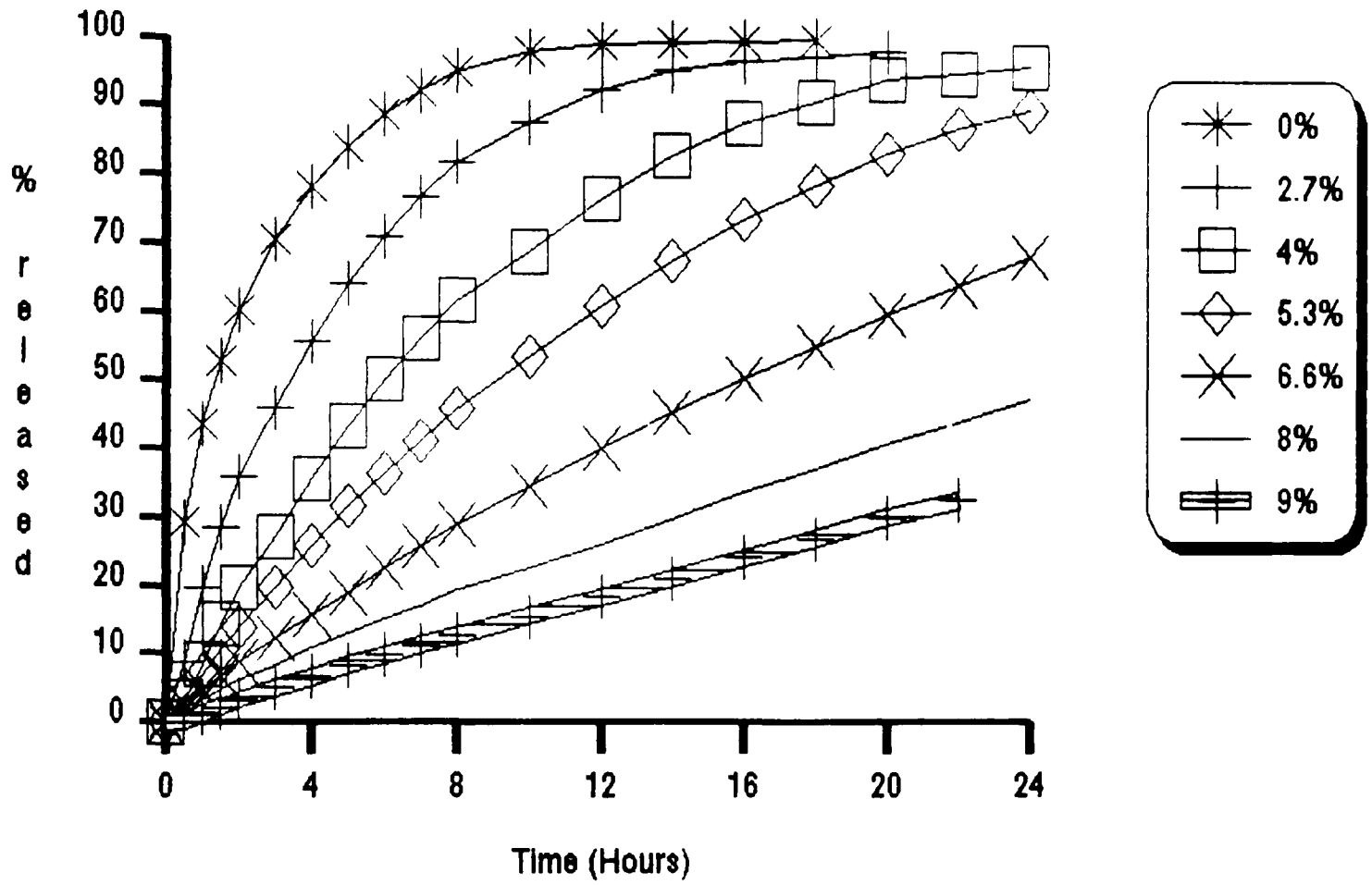


Figure 4.9. *In-vitro* drug release from 800mg of ibuprofen pellets containing 70%w/w ibuprofen (expressed as % weight dry solids in uncoated formulation) coated with an *x*% weight increase (see key), applied as an aqueous polymeric dispersion containing Eudragit RS/RL30D.

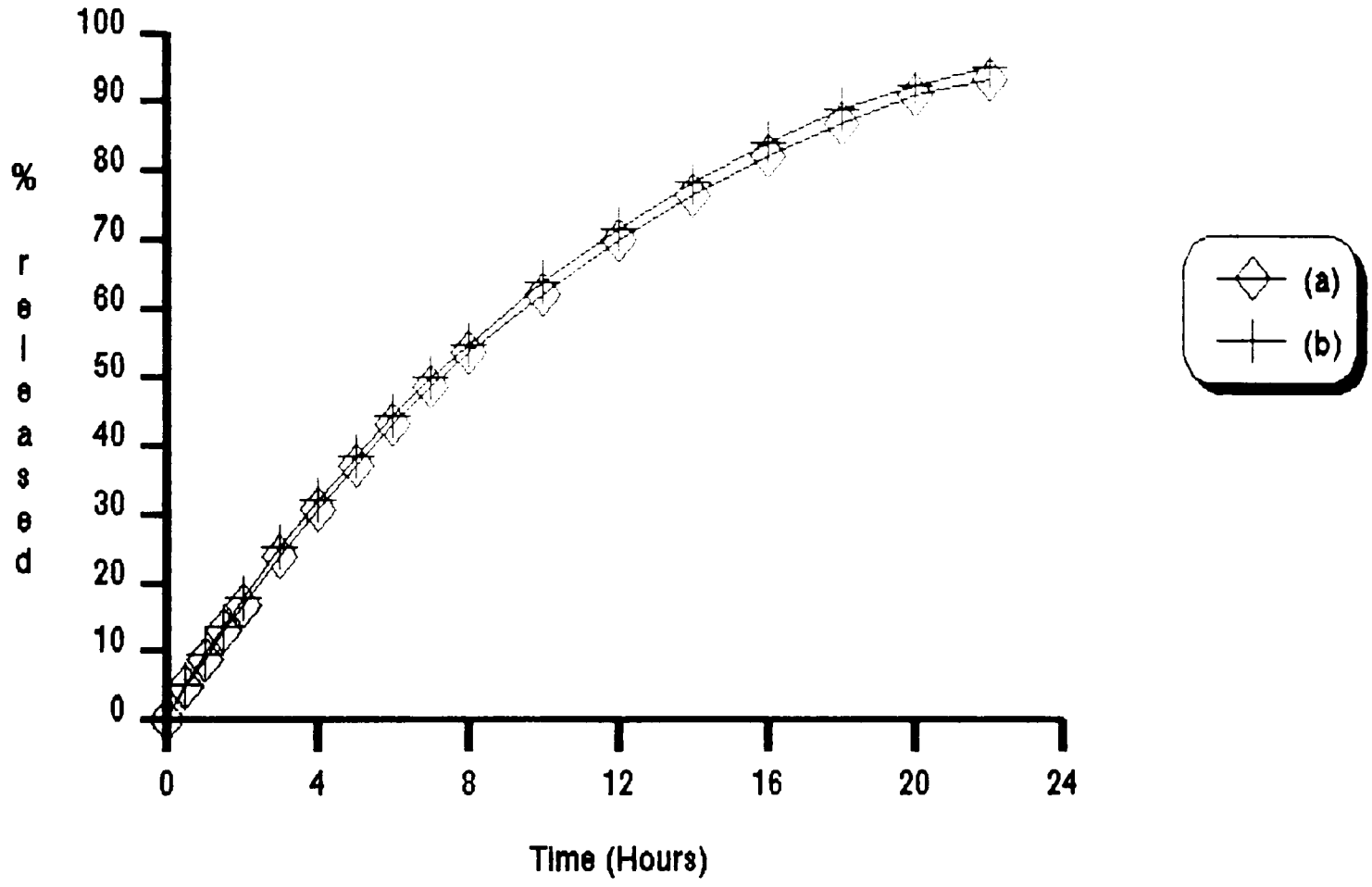


Figure 4.10. *In-vitro* drug release from 800mg of ibuprofen pellets containing 70%w/w ibuprofen (expressed as % weight dry solids in uncoated formulation) coated with a 5.3% weight increase, applied as an aqueous polymeric dispersion containing Eudragit RS/RL30D; (a) pellets subjected to a post-coating "curing" stage; (b) pellets not subjected to a post-coating "curing" stage.

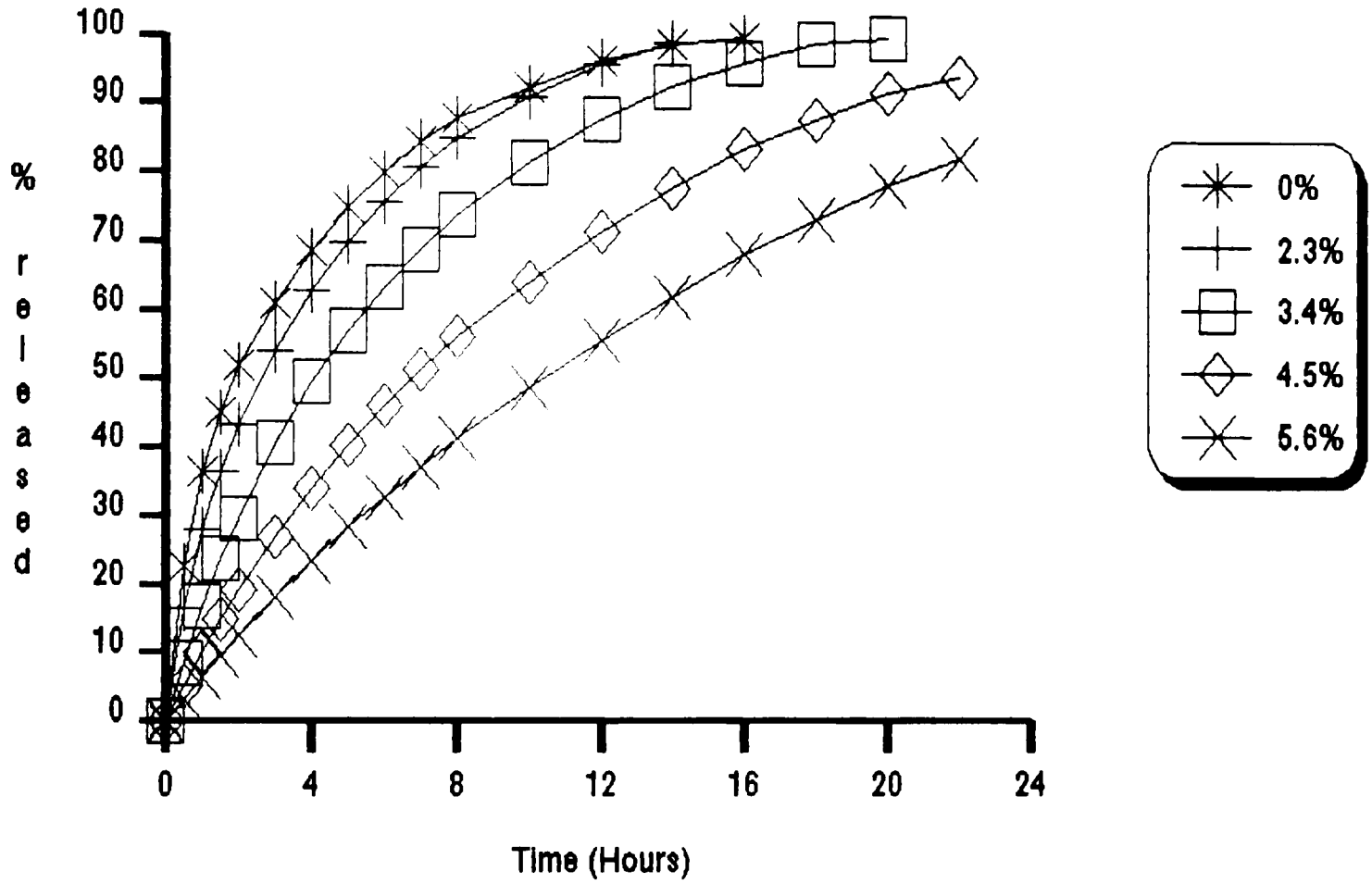


Figure 4.11. *In-vitro* drug release from 800mg of ibuprofen pellets containing 60%w/w ibuprofen (expressed as % weight dry solids in uncoated formulation) coated with an *x*% weight increase (see key), applied as an aqueous polymeric dispersion containing Eudragit RS/RL30D.

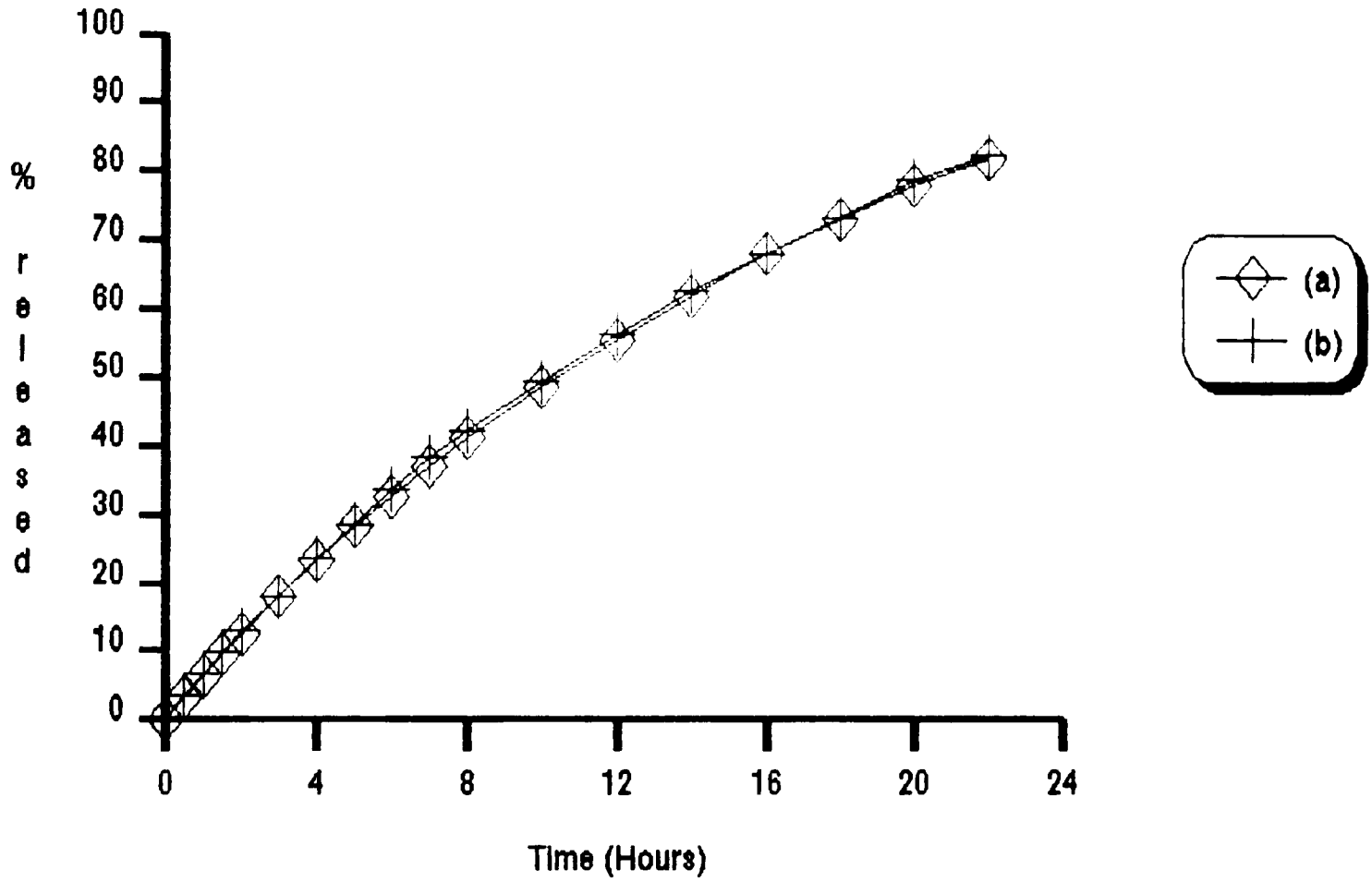


Figure 4.12. *In-vitro* drug release from 800mg of ibuprofen pellets containing 60%w/w ibuprofen (expressed as % weight dry solids in uncoated formulation) coated with a 5.6% weight increase, applied as an aqueous polymeric dispersion containing Eudragit RS/RL30D; (a) pellets subjected to a post-coating "curing" stage; (b) pellets not subjected to a post-coating "curing" stage.

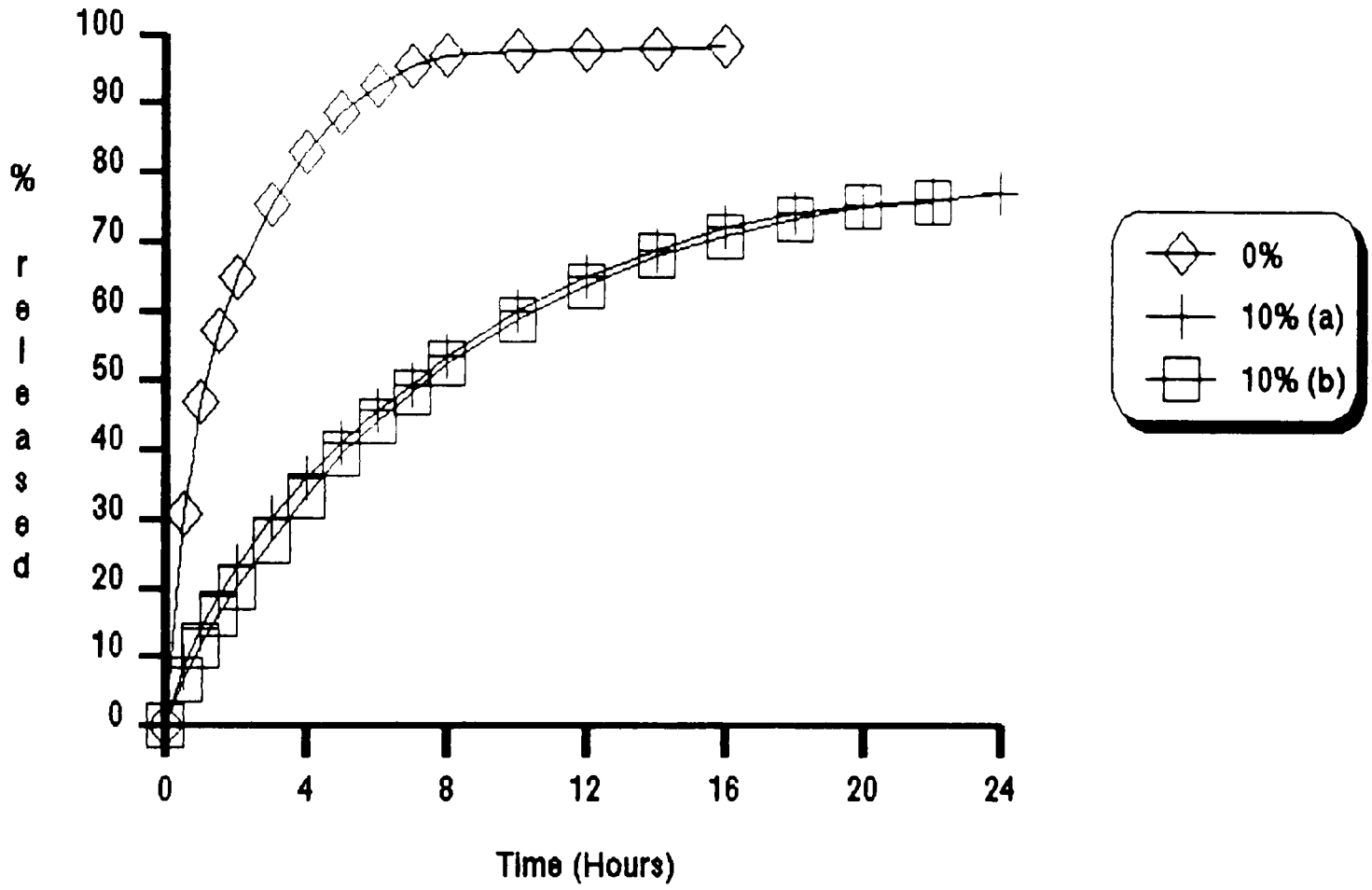


Figure 4.13. *In-vitro* drug release from 800mg of ibuprofen pellets containing 80%w/w ibuprofen (expressed as % weight dry solids in uncoated formulation), coated with a 10% weight increase applied as an aqueous polymeric dispersion containing Surelease; (a) pellets subjected to a post-coating "curing" stage; (b) pellets not subjected to a post-coating "curing" stage.

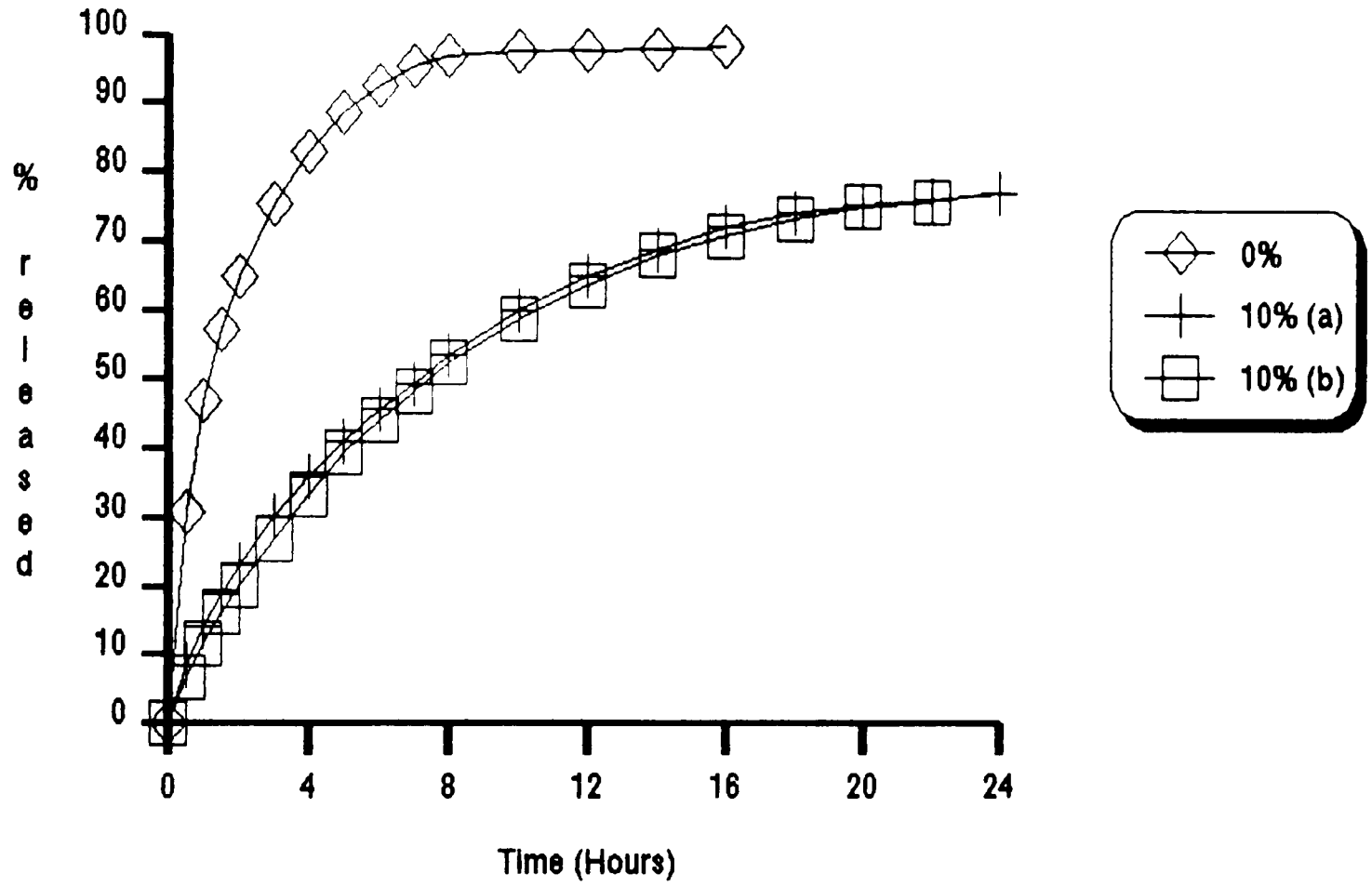


Figure 4.13. *In-vitro* drug release from 800mg of ibuprofen pellets containing 80%w/w ibuprofen (expressed as % weight dry solids in uncoated formulation), coated with a 10% weight increase applied as an aqueous polymeric dispersion containing Surelease; (a) pellets subjected to a post-coating "curing" stage; (b) pellets not subjected to a post-coating "curing" stage.

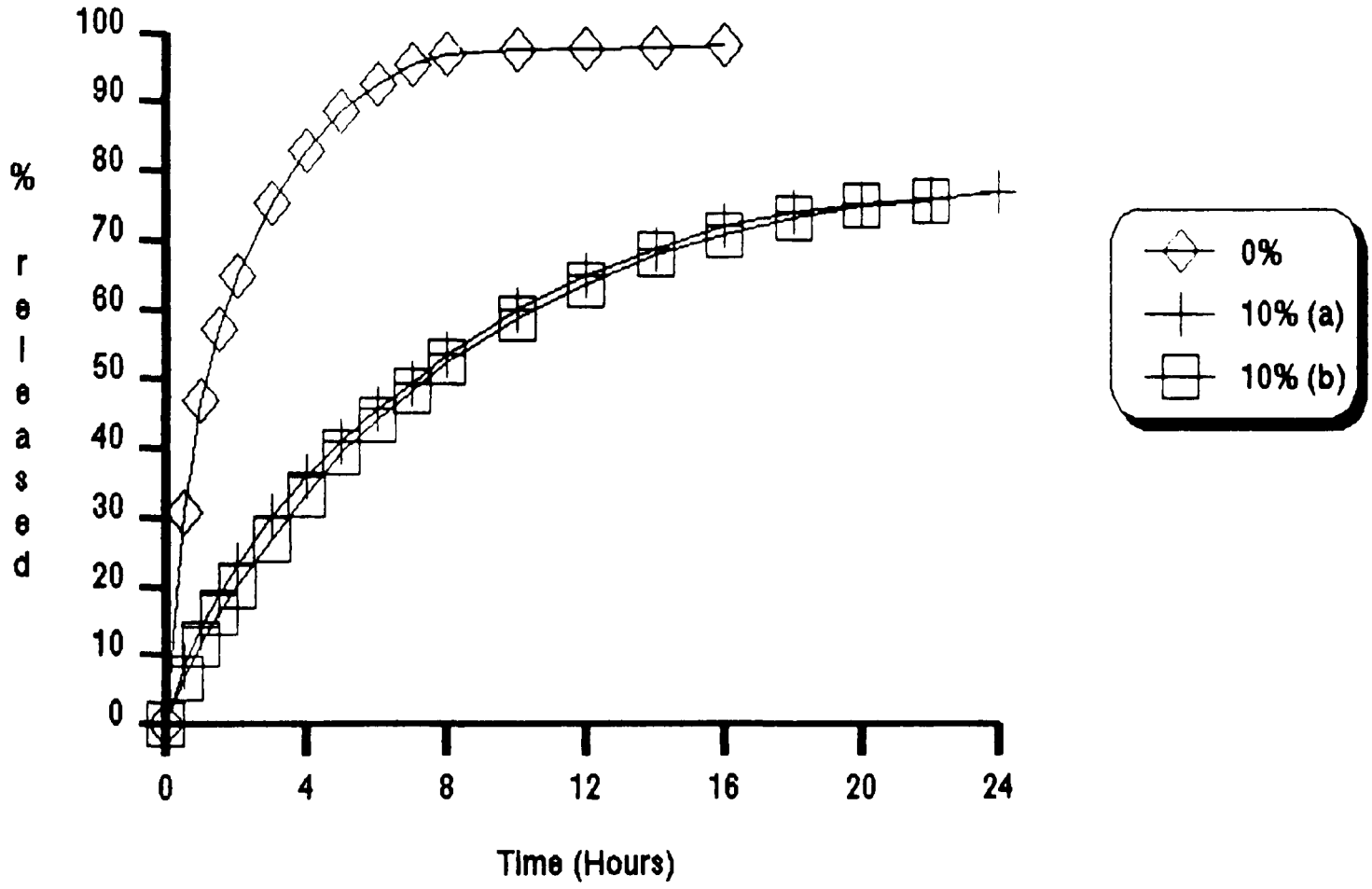


Figure 4.13. *In-vitro* drug release from 800mg of ibuprofen pellets containing 80%w/w ibuprofen (expressed as % weight dry solids in uncoated formulation), coated with a 10% weight increase applied as an aqueous polymeric dispersion containing Surelease; (a) pellets subjected to a post-coating "curing" stage; (b) pellets not subjected to a post-coating "curing" stage.

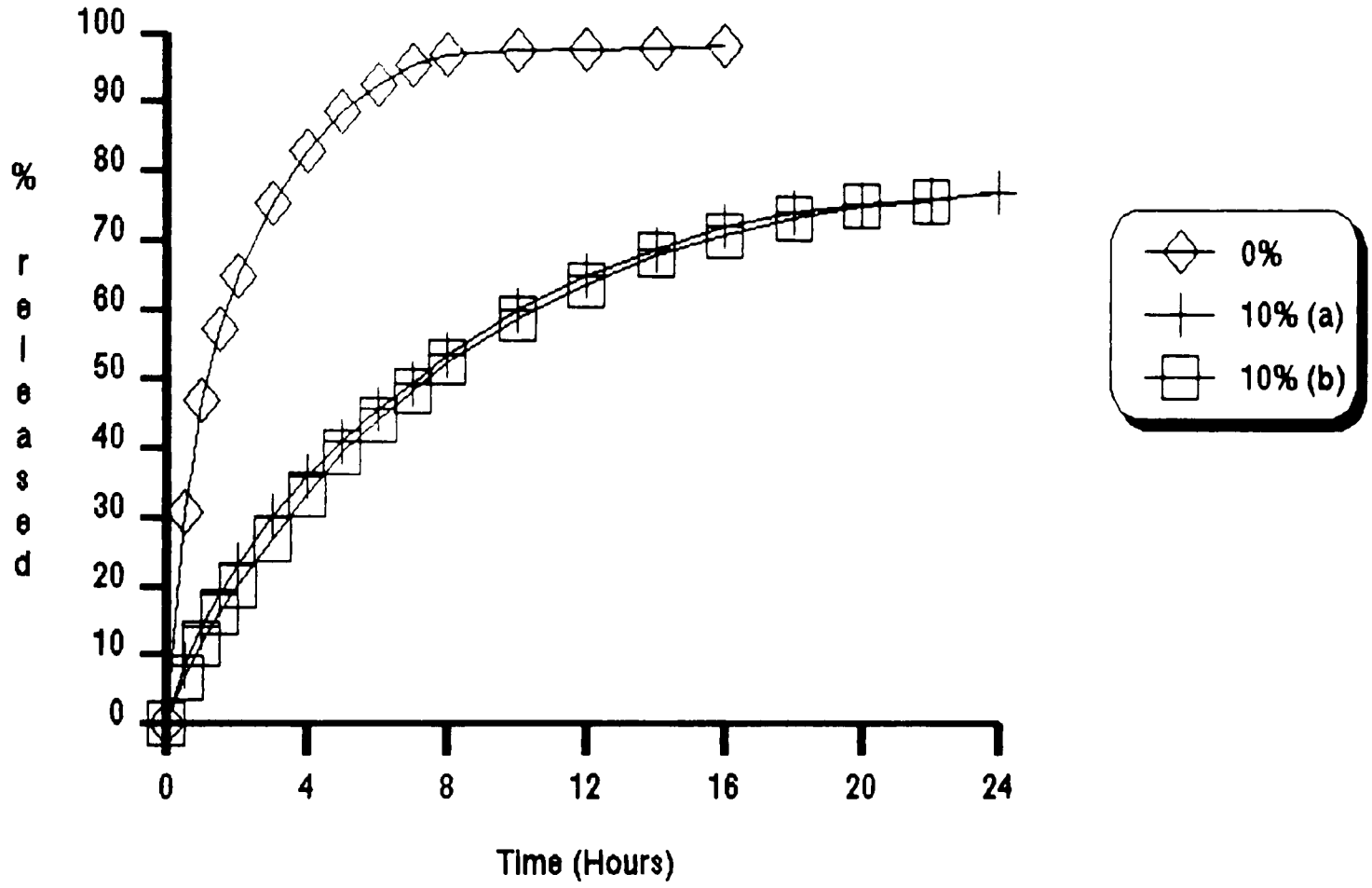


Figure 4.13. *In-vitro* drug release from 800mg of ibuprofen pellets containing 80%w/w ibuprofen (expressed as % weight dry solids in uncoated formulation), coated with a 10% weight increase applied as an aqueous polymeric dispersion containing Surelease; (a) pellets subjected to a post-coating "curing" stage; (b) pellets not subjected to a post-coating "curing" stage.

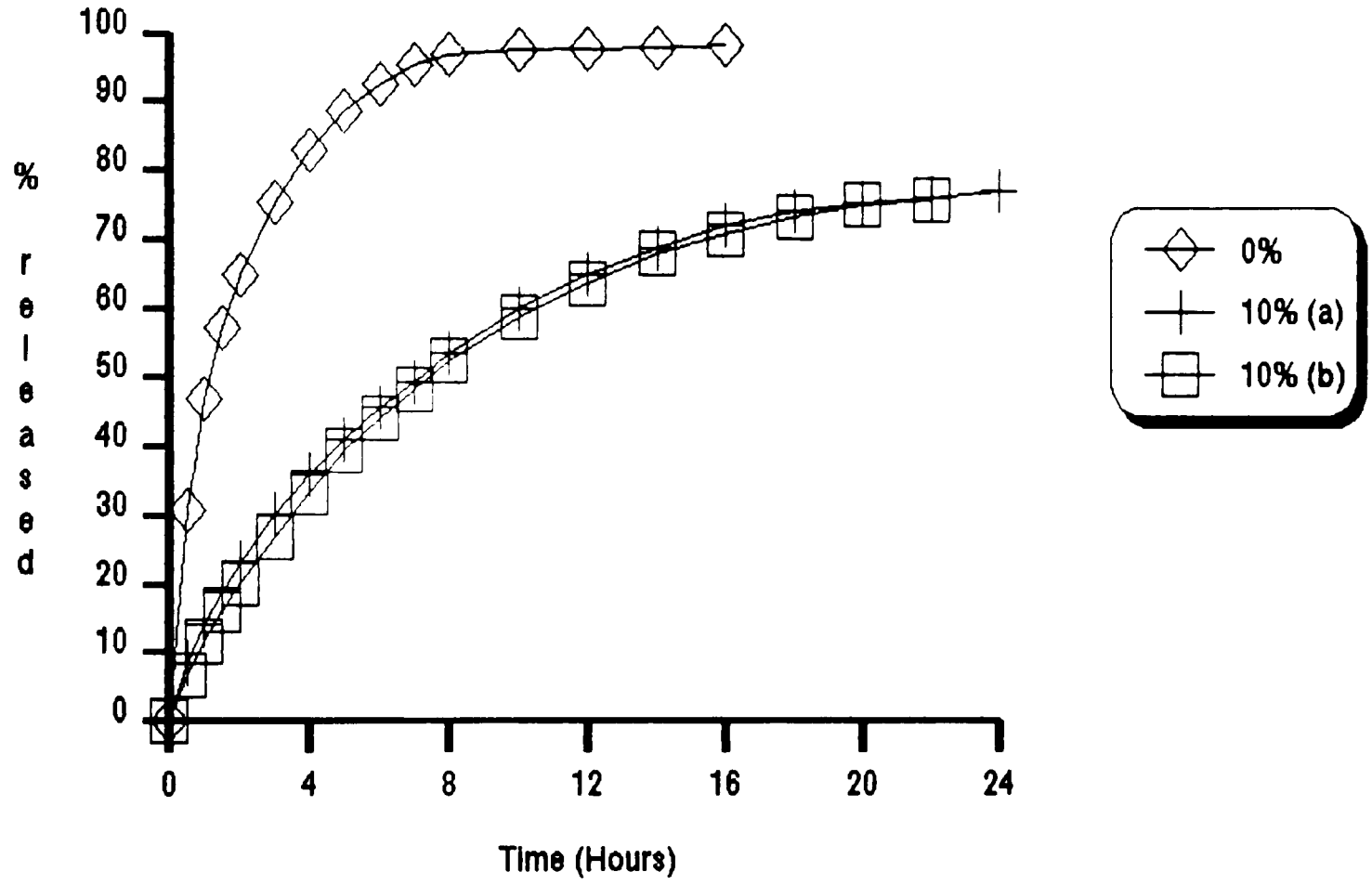


Figure 4.13. *In-vitro* drug release from 800mg of ibuprofen pellets containing 80%w/w ibuprofen (expressed as % weight dry solids in uncoated formulation), coated with a 10% weight increase applied as an aqueous polymeric dispersion containing Surelease; (a) pellets subjected to a post-coating "curing" stage; (b) pellets not subjected to a post-coating "curing" stage.

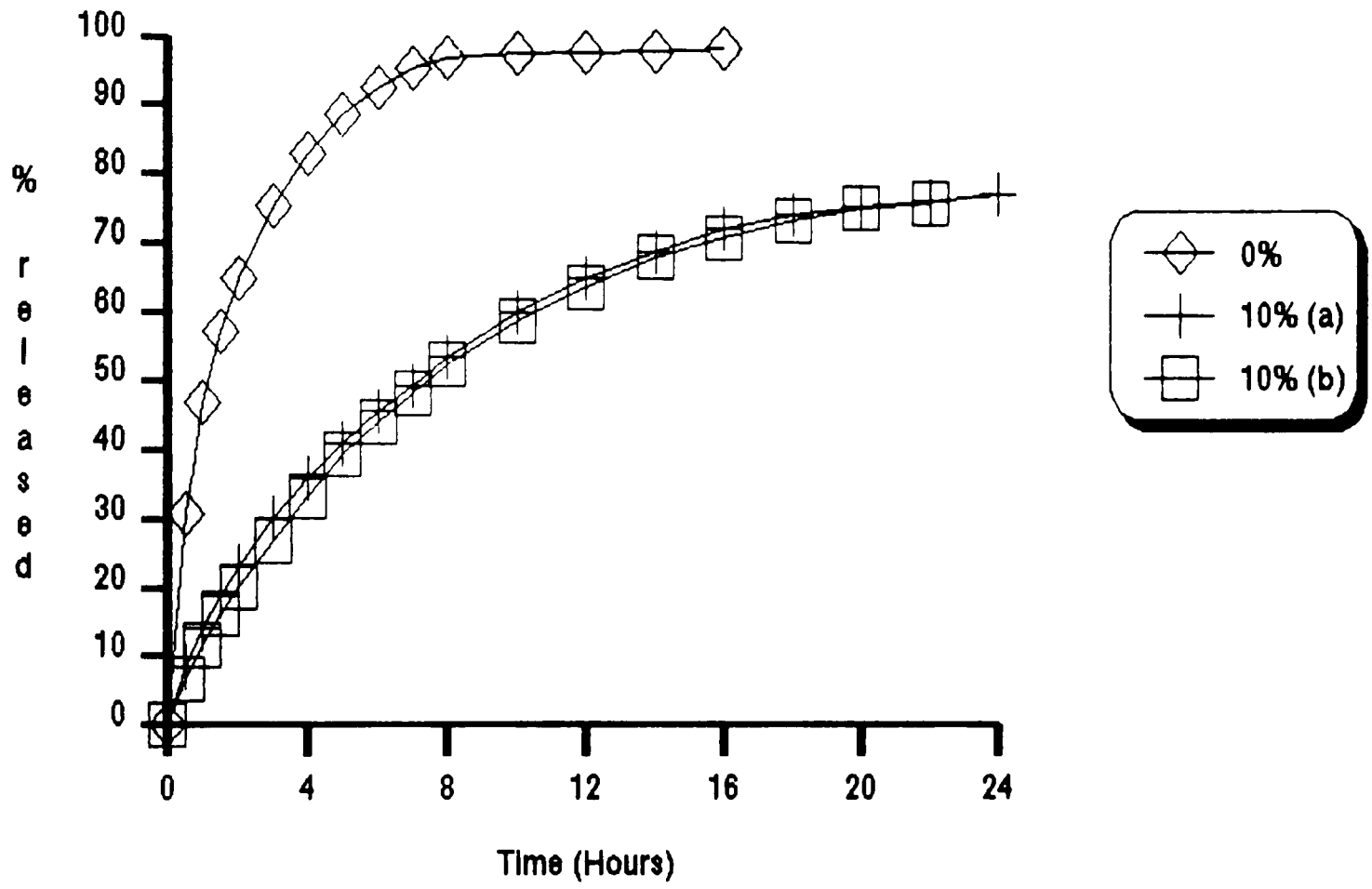


Figure 4.13. *In-vitro* drug release from 800mg of ibuprofen pellets containing 80%w/w ibuprofen (expressed as % weight dry solids in uncoated formulation), coated with a 10% weight increase applied as an aqueous polymeric dispersion containing Surelease; (a) pellets subjected to a post-coating "curing" stage; (b) pellets not subjected to a post-coating "curing" stage.

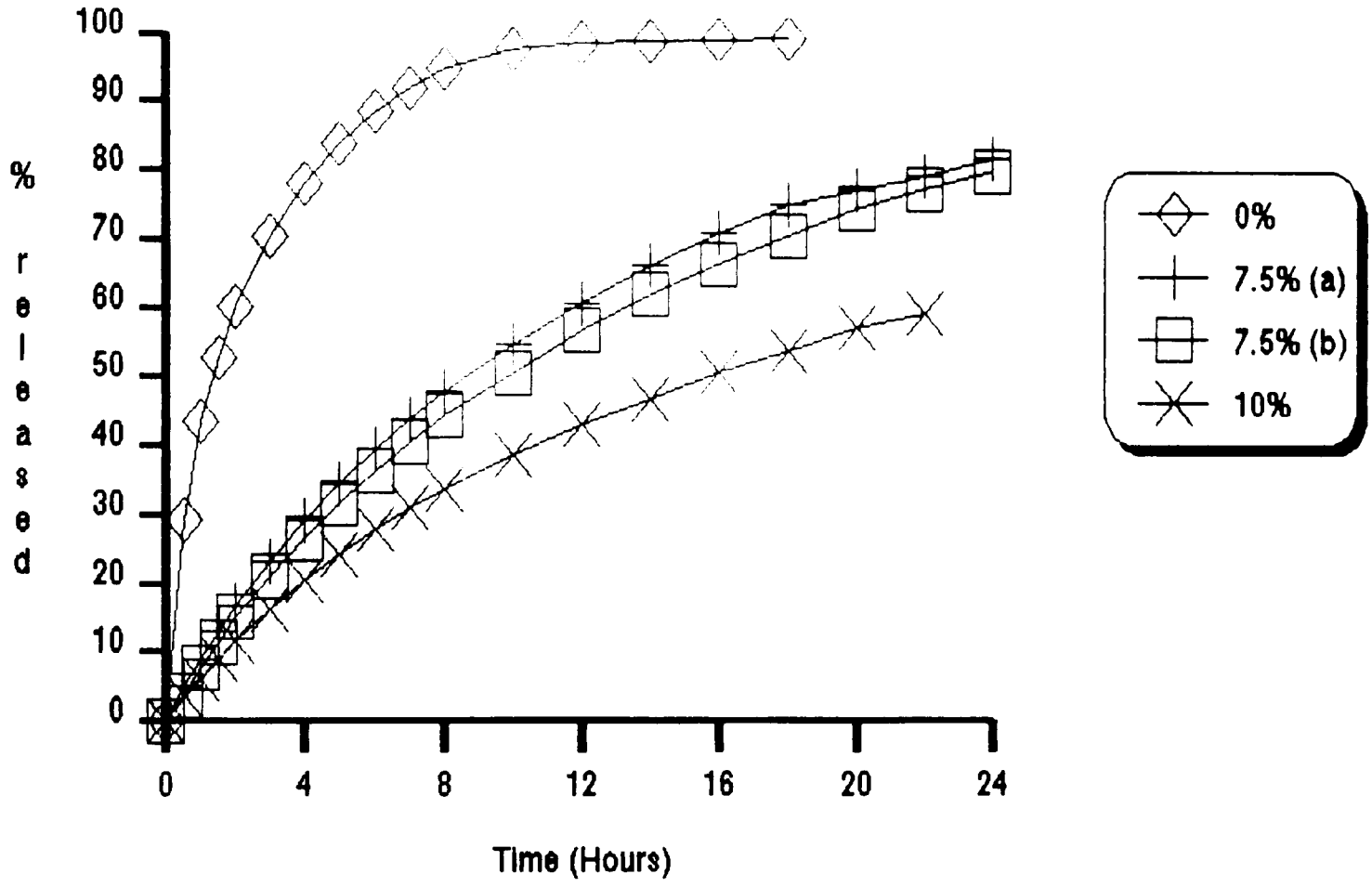


Figure 4.14. *In-vitro* drug release from 800mg of ibuprofen pellets containing 70%w/w ibuprofen (expressed as % weight dry solids in uncoated formulation), coated with 7.5% and 10% weight increases, applied as an aqueous polymeric dispersion containing Surelease; (a) pellets subjected to a post-coating "curing" stage; (b) pellets not subjected to a post-coating "curing" stage.

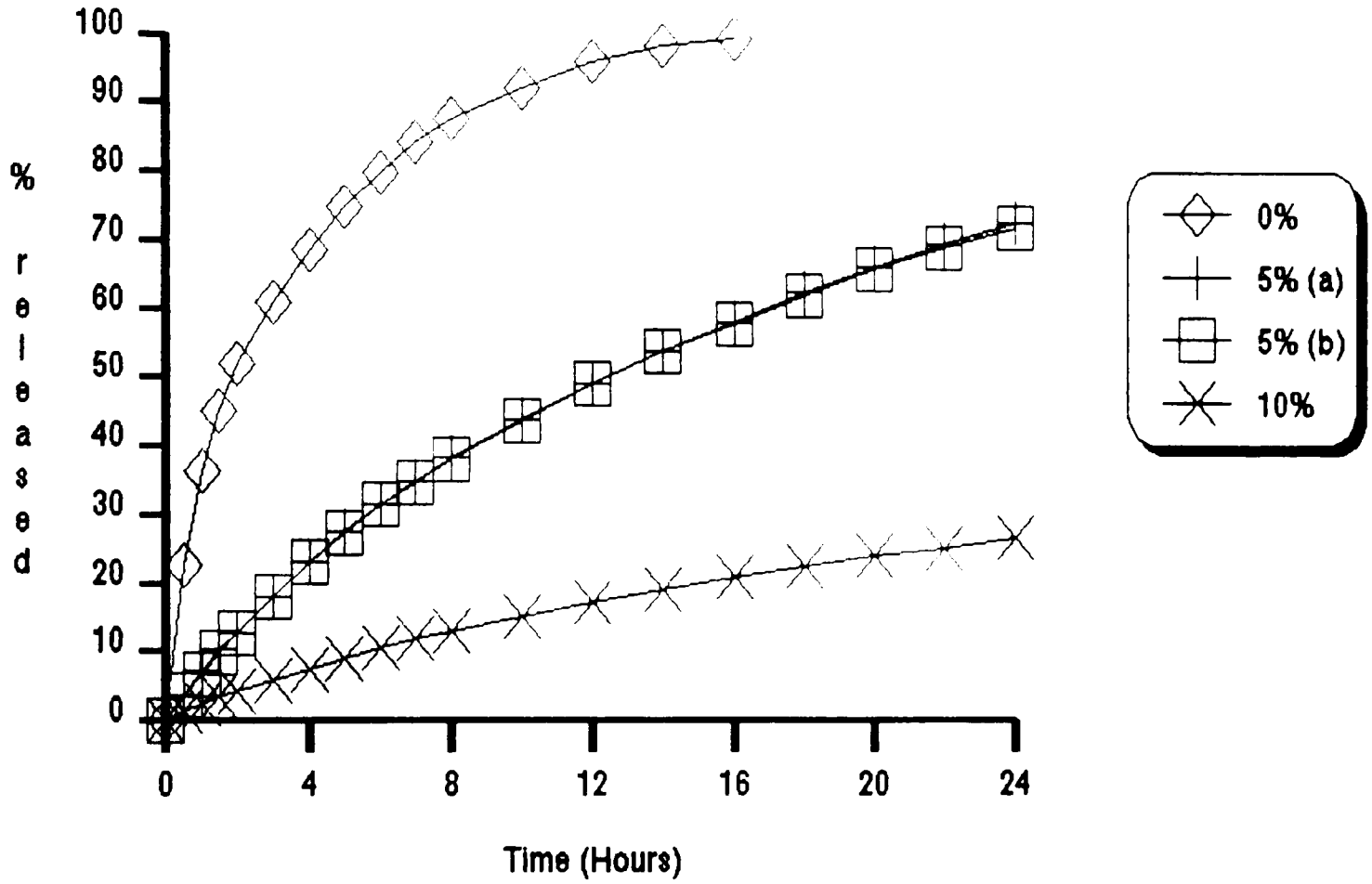


Figure 4.15. *In-vitro* drug release from 800mg of ibuprofen pellets containing 60%w/w ibuprofen (expressed as % weight dry solids in uncoated formulation), coated with 5% and 10% weight increases, applied as an aqueous polymeric dispersion containing Surelease; (a) pellets subjected to a post-coating "curing" stage; (b) pellets not subjected to a post-coating "curing" stage.

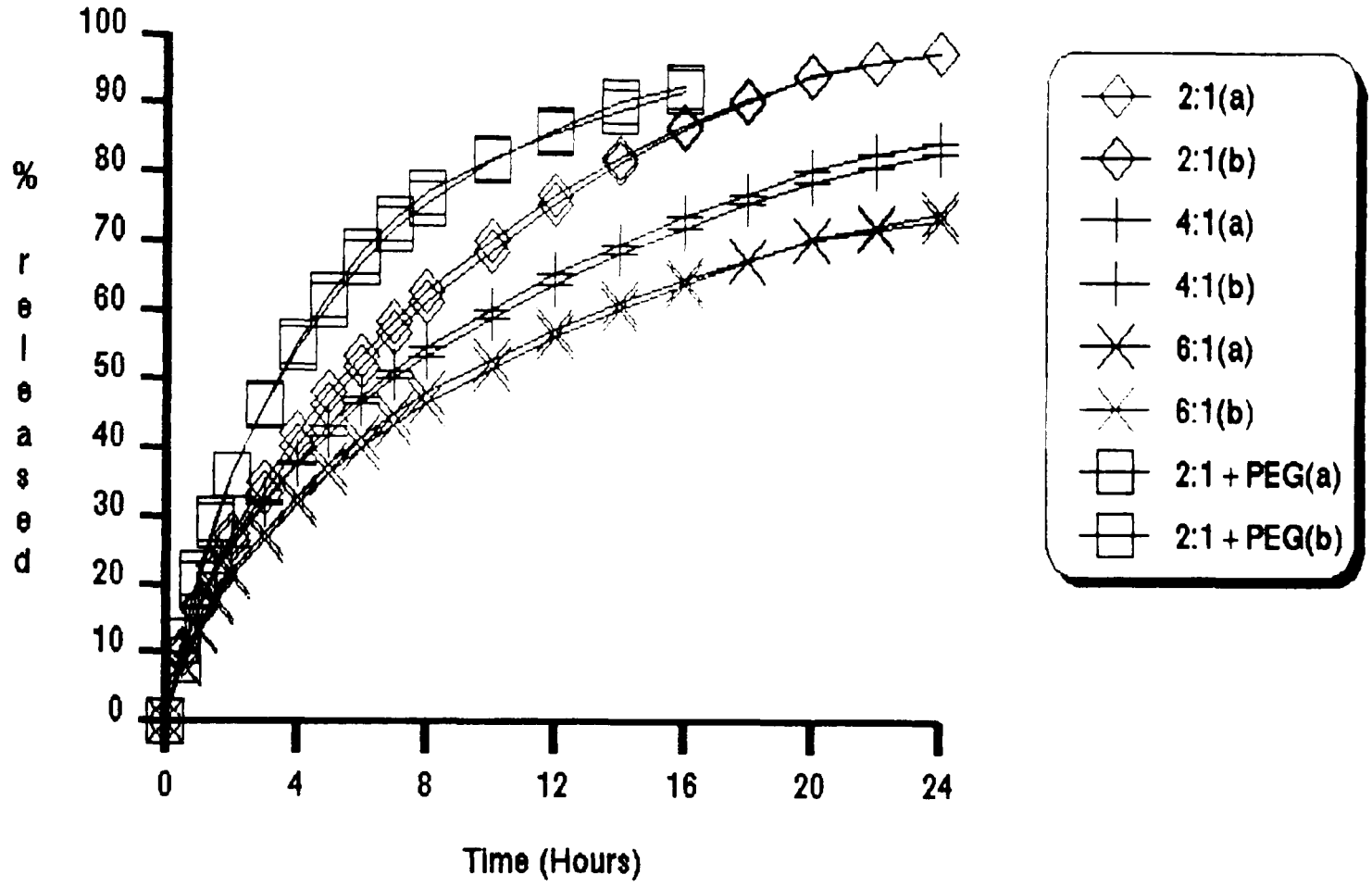


Figure 4.16. *In-vitro* drug release from 800mg of ibuprofen pellets containing 80%w/w ibuprofen (expressed as % weight dry solids in uncoated formulation) coated with a 10% weight increase, applied as an aqueous polymeric dispersion containing Silicone Elastomer; (a) pellets subjected to a post-coating "curing" stage; (b) pellets not subjected to a post-coating "curing" stage. The ratio of Silicone Emulsion:Colloidal Silica in the coating formulation is given in the key; one of the coating formulations contains PEG 6000 BP (polyethylene glycol) 10%w/w, as a plasticiser.

As discussed in some detail in section 3.1 it is essential that polymer coalescence and complete film formation is achieved during the film coating process with these aqueous polymeric dispersions. Coated pellets were therefore subjected to an additional "curing" stage of 24 hours in a hot air oven at 40°C. All profiles shown represent drug release from pellets which have been subjected to this "curing" procedure. As a control, samples of coated pellets from each batch were not exposed to this additional "curing" stage. Those *in-vitro* release profiles for which the additional "curing" stage was not part of the manufacturing process are given the nomenclature of profile (b), (Figures 4.8, 4.10, 4.12, 4.13, 4.14, 4.15, 4.16). It is evident from those figures showing the *in-vitro* release profiles for coated pellets not subjected to the "curing" process, that complete film formation and polymer coalescence is occurring during the coating process under the drying conditions of the coating chamber. This may be concluded as a consequence of the negligible difference in the *in-vitro* drug release profiles obtained from both tray dried and control samples within this study.

In-vitro drug release from uncoated pellets containing 80%w/w ibuprofen and coated with silicone elastomer is shown in Figure 4.16. Again by exposing these pellets to an additional "curing" stage, it is apparent that complete polymer coalescence occurs during the coating process; this supports the claim by Dow Corning in their product literature that this is the case.

Comparison of the *in-vitro* release of ibuprofen from those pellets coated with a Silicone Elastomer dispersion containing a ratio of silicone emulsion:colloidal silica of 2:1, with and without the incorporation of plasticiser, polyethylene glycol (PEG 6000) 10%w/w, results as anticipated, in an enhanced rate of drug release. It is therefore apparent, that a consequence of incorporating plasticiser in

such a polymeric membrane surrounding multiparticulates which are essentially homogeneous matrices in their uncoated form, is an enhanced rate of drug release. This enables postulation that diffusion of solute drug molecules through plasticiser channels created as a consequence of the pore-forming properties of an incorporated plasticiser within the otherwise impermeable membrane, is at the very least, contributing to the mechanism of drug release from such a system.

The effect of increasing the ratio of silicone to silica leads to a corresponding reduction in the rate of drug release (Figure 4.16). Increasing the silicone content of the dispersion with a corresponding decrease in the content of the colloidal silica, enhances release retarding capacity of the membrane.

In summary, the presence of plasticiser or a reduction in the ratio of silicone to silica, will have the effect of increasing the rate of drug release by increasing the permeability of the polymeric membrane.

A further consequence of incorporating polyethylene glycol 6000 in the coating formulation and/or of increasing the silicone content, is a degree of sticking and pellet agglomeration during the coating process under the equilibrium conditions within the coating chamber. As a consequence of this it was not possible to successfully coat pellets with a dispersion containing a ratio of silicone:silica greater than 6:1, nor with a dispersion containing PEG 6000 in any formulation with a higher ratio of silicone:silica than 2:1.

In short, the presence of plasticiser or an increase in the silicone content within the coating formulation, leads to sticking and a real danger of pellet agglomeration during the coating process. The waxy nature of polyethylene glycol under the drying conditions within the coating chamber is particularly highlighted in the coating of small particles. As a result of the physical size and density of these pellets, any tendency for sticking is immediately evident in the form of

agglomeration. Once this has occurred within the coating chamber it is necessary to discard the batch, since uneven application of film coating dispersion is the primary consequence of poor, inadequate or incomplete fluidisation of the chamber contents.

Within the scope of this work both uncoated and coated pellets containing ibuprofen and pellets post *in-vitro* dissolution testing, have been examined by scanning electron microscopy (SEM), in an attempt to understand more fully the drug release mechanism(s) from uncoated and coated pellets.

4.3.3. Qualitative evaluation of pellet and film coat appearance using scanning electron microscopy (SEM).

Uncoated and coated pellets containing ibuprofen have been examined by scanning electron microscopy in terms of pellet surface and pellet cross-sectional characteristics. In an attempt to elucidate the mechanism(s) controlling drug release from pellets, which in the uncoated form are essentially homogeneous matrix multiparticulates, pellets, both uncoated and coated and pre and post *in-vitro* dissolution testing, have been examined closely in respect of these two parameters.

4.3.3.1. Effect of uncoated pellet potency on the surface characteristics of ibuprofen pellets prior to and following drug removal by *in-vitro* dissolution.

Figures 4.17 to 4.20 inclusive show scanning electron micrographs (SEMs) of the surface appearance of uncoated pellets containing ibuprofen, both before and after drug removal by *in-vitro* dissolution testing. Two pellet potencies have been examined within this section, namely pellets containing 80%w/w and those containing 60%w/w drug with Avicel PH101 (expressed as per cent weight dry solids).

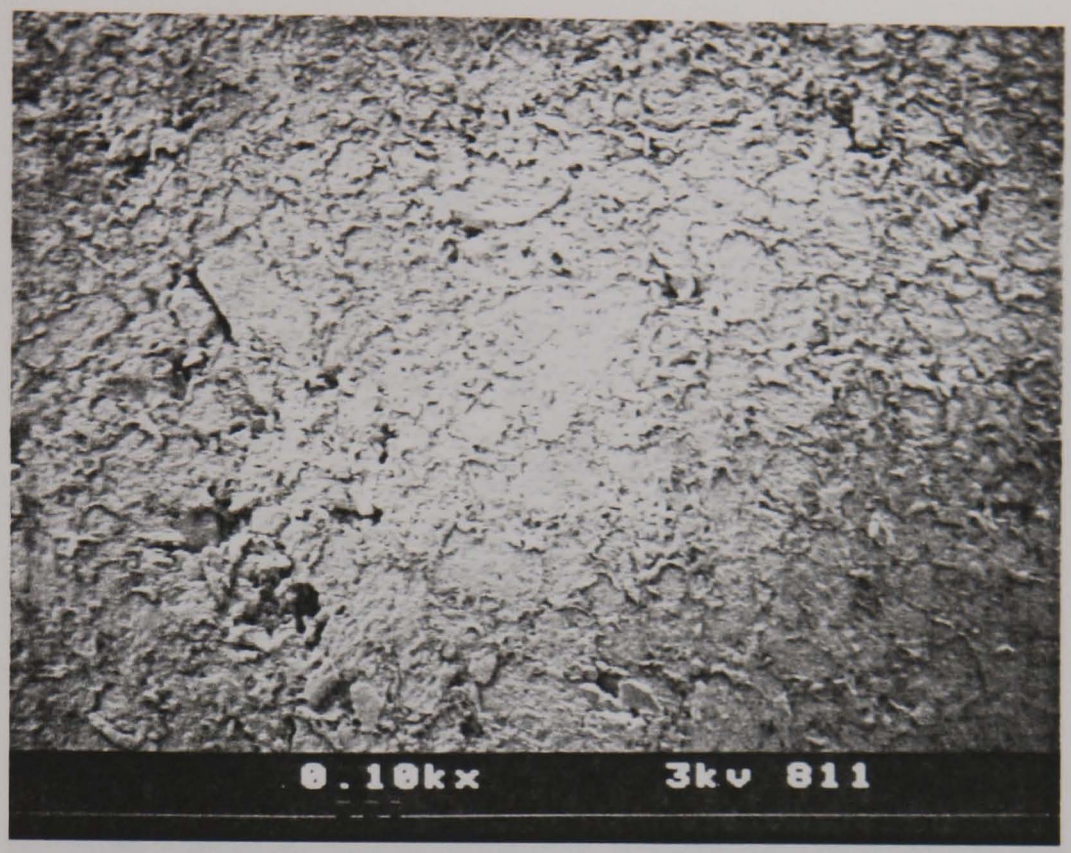


Figure 4.17a. SEM of uncoated pellet surface containing 80% ibuprofen (pre-dissolution); x400.

Figure 4.17b. SEM of uncoated pellet surface containing 80% ibuprofen (pre-dissolution); x800.

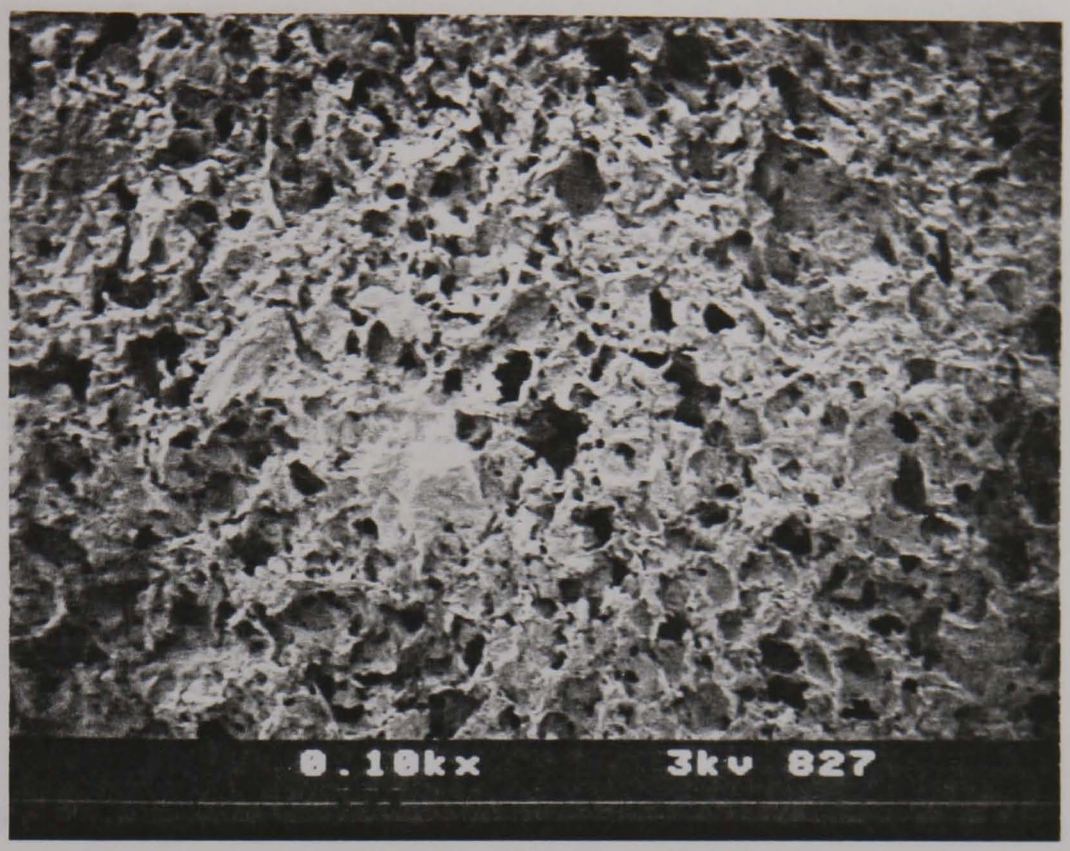


Figure 4.18a. SEM of uncoated pellet surface containing 80% ibuprofen (post-dissolution); x400.

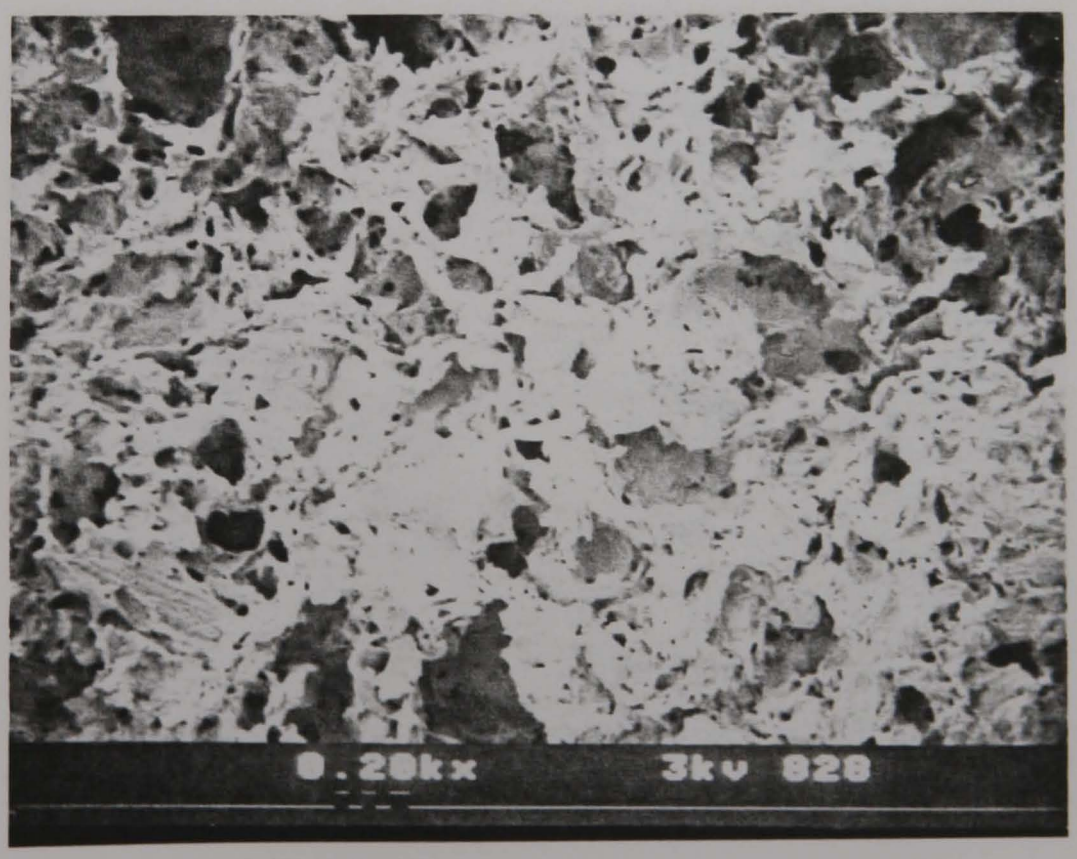


Figure 4.18b. SEM of uncoated pellet surface containing 80% ibuprofen (post-dissolution); x800.

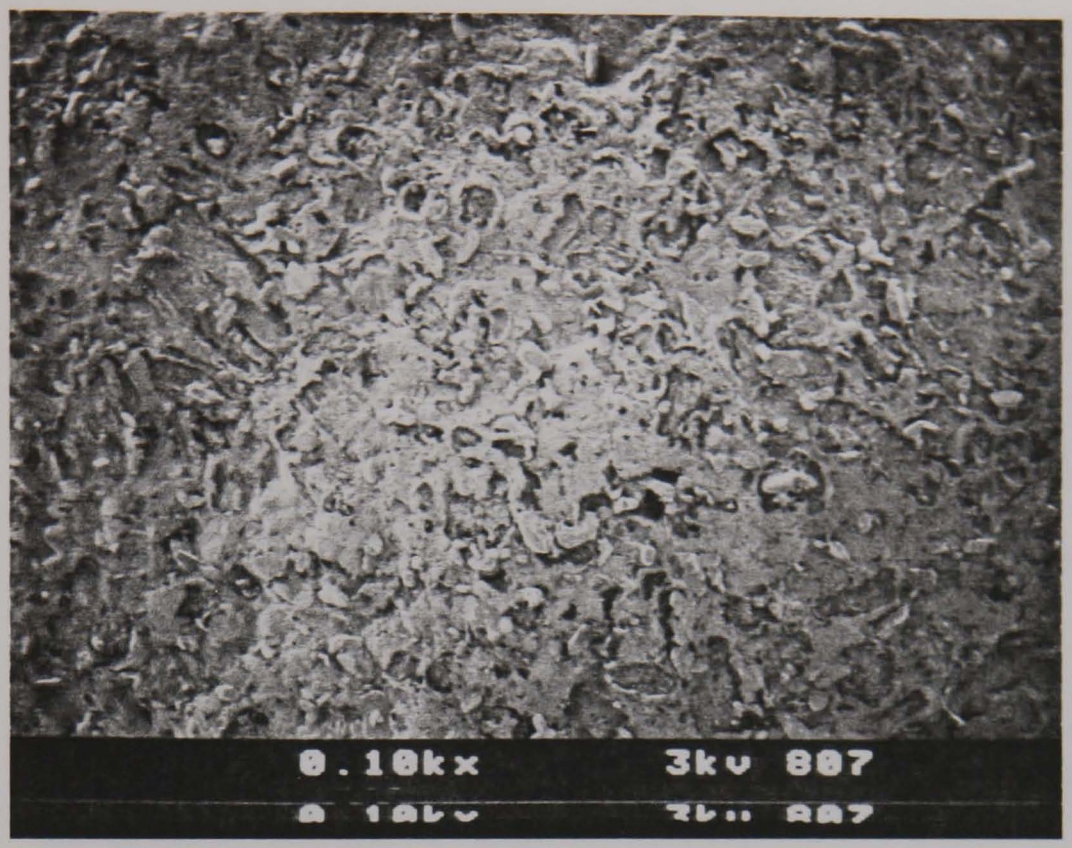


Figure 4.19a. SEM of uncoated pellet surface containing 60% ibuprofen (pre-dissolution); x400.

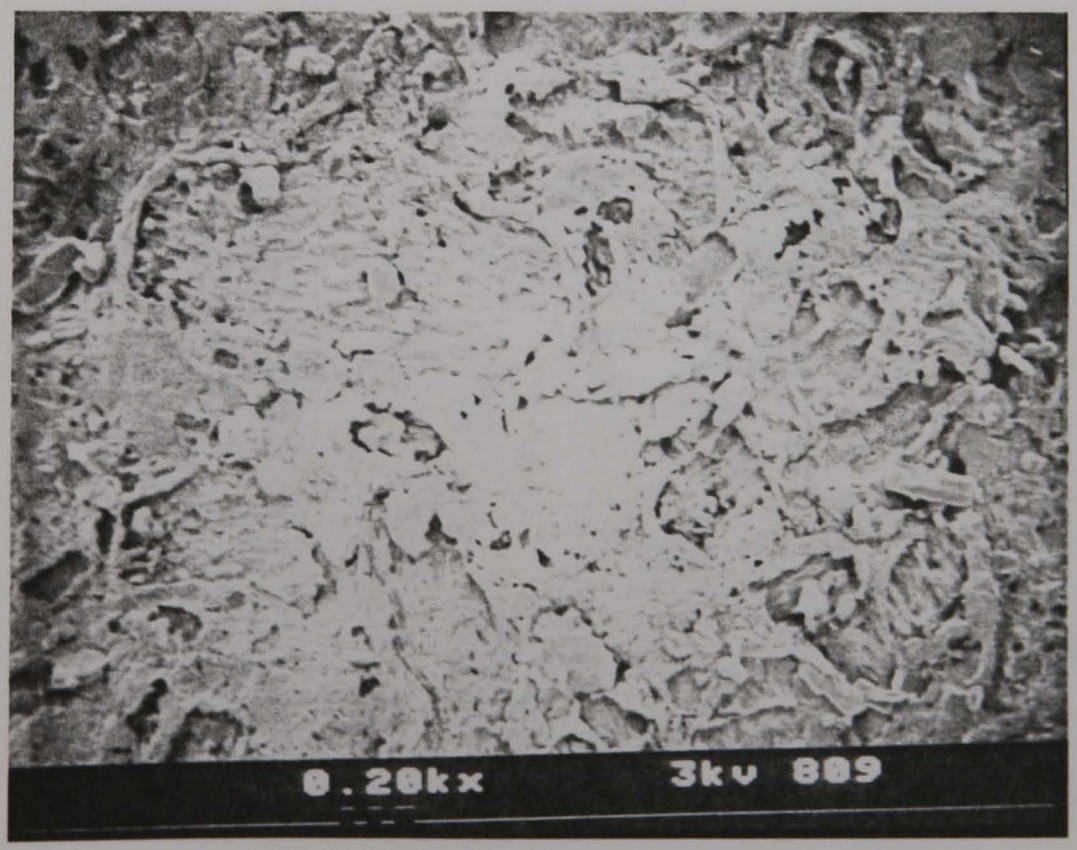


Figure 4.19b. SEM of uncoated pellet surface containing 60% ibuprofen (pre-dissolution); x800.

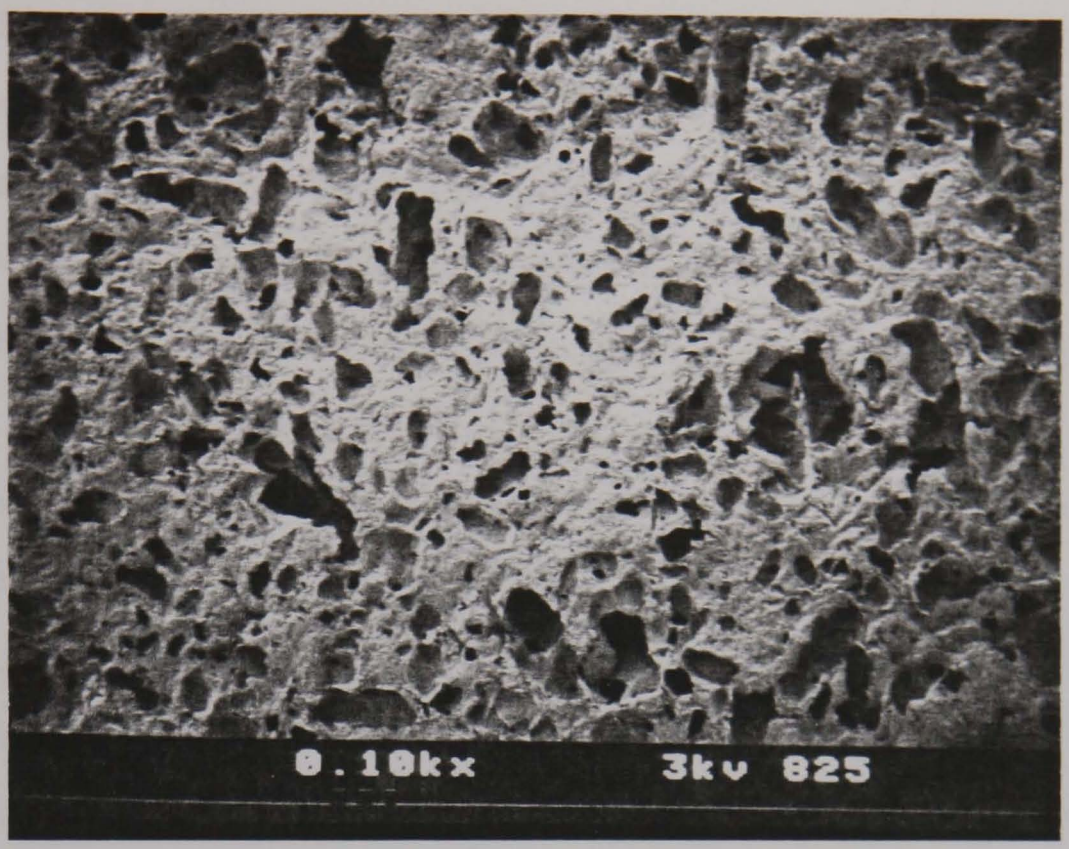


Figure 4.20a. SEM of uncoated pellet surface containing 60% ibuprofen (post-dissolution); x400.

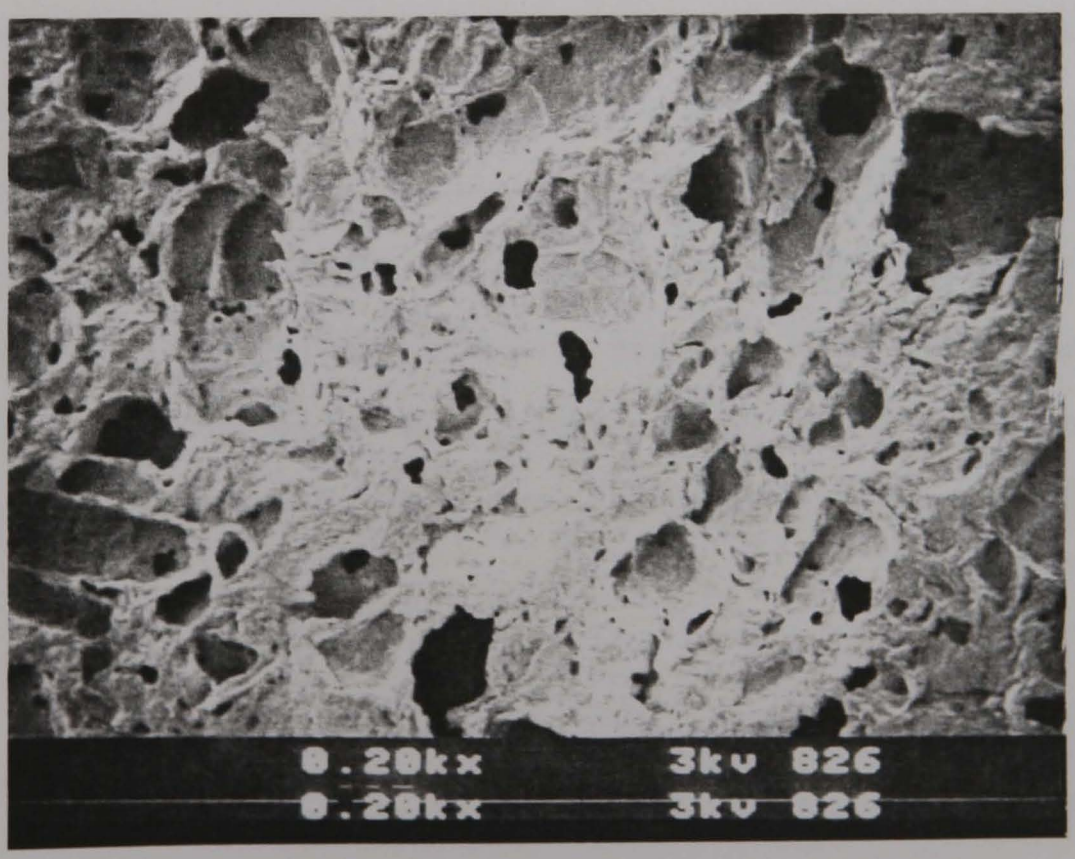


Figure 4.20b. SEM of uncoated pellet surface containing 60% ibuprofen (post-dissolution); x800.

Comparison of the surface characteristics of the two uncoated pellet formulations (Figures 4.17 and 4.19) prior to dissolution testing, indicates very little visible difference. The spheronisation processing variables used in the preparation of these two uncoated pellet formulations were similar and one might therefore anticipate that the resultant surface characteristics, in spite of different drug loading, would be similar. This is evidently the case.

In-vitro dissolution testing of uncoated pellets (even those containing only 20%w/w microcrystalline cellulose) yields visibly intact entities; pellets were removed from the dissolution vessels following removal of the drug, allowed to dry under ambient conditions on a Whatman filter paper and subsequently examined by scanning electron microscopy. Figures 4.18 and 4.20 admirably illustrate the structural skeletal matrix network of the spheronisation enhancer, microcrystalline cellulose. The voids created in the pellet surface by drug removal from those pellets initially containing 80%w/w ibuprofen, are more profuse; this is as a consequence of the product initially housing a greater drug loading. The resultant uncoated pellet surfaces are sponge-like in appearance. It is worthy of mention that the distribution of this inert component is extremely regular; one might therefore postulate that the distribution of ibuprofen within the pellets initially was also favourable. The voids created as a consequence of drug removal in the pellet surfaces, are not only evenly distributed but are also of regular size for any given drug loading.

4.3.3.2. Effect of uncoated pellet potency on the cross-sectional characteristics of ibuprofen pellets prior to and following drug removal by *in-vitro* dissolution.

Figures 4.21 to 4.24 inclusive show SEMs of the cross-sections of uncoated ibuprofen pellets both prior to and after drug removal.

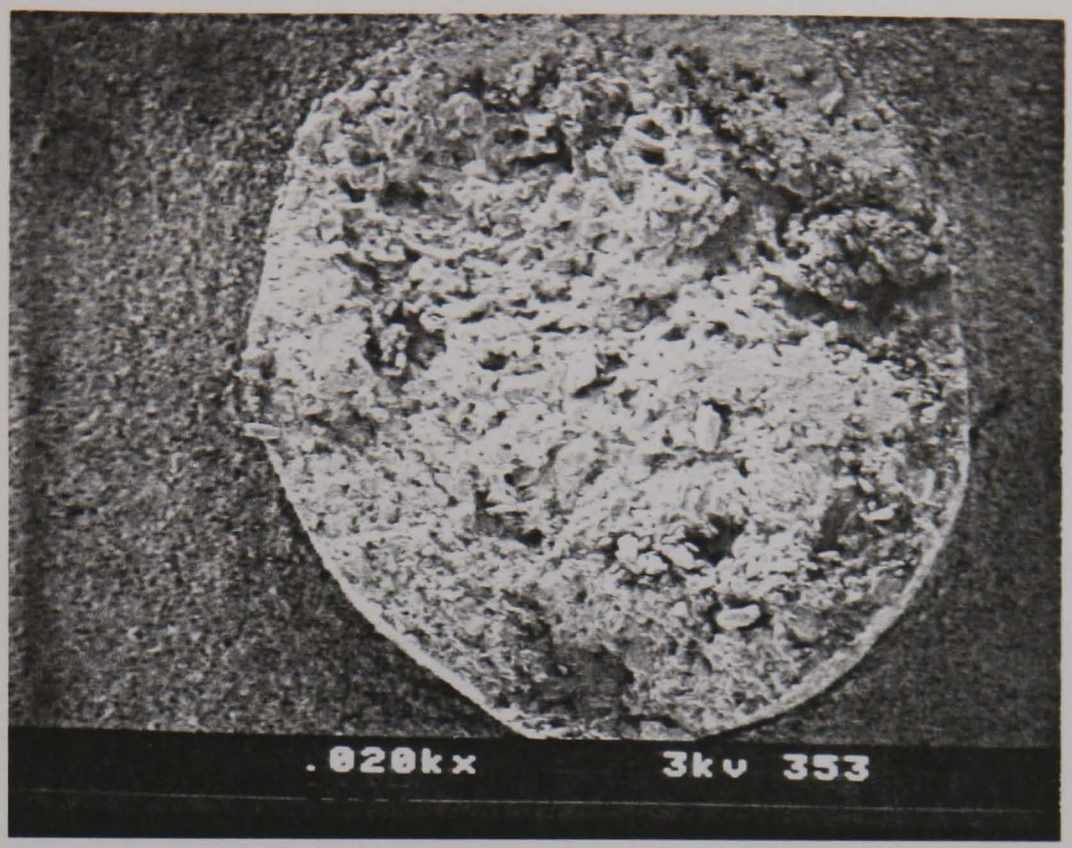


Figure 4.21a. SEM of uncoated pellet cross-section containing 80% ibuprofen (pre-dissolution); x80.

Figure 4.21b. SEM of uncoated pellet cross-section containing 80% ibuprofen (pre-dissolution); x400.

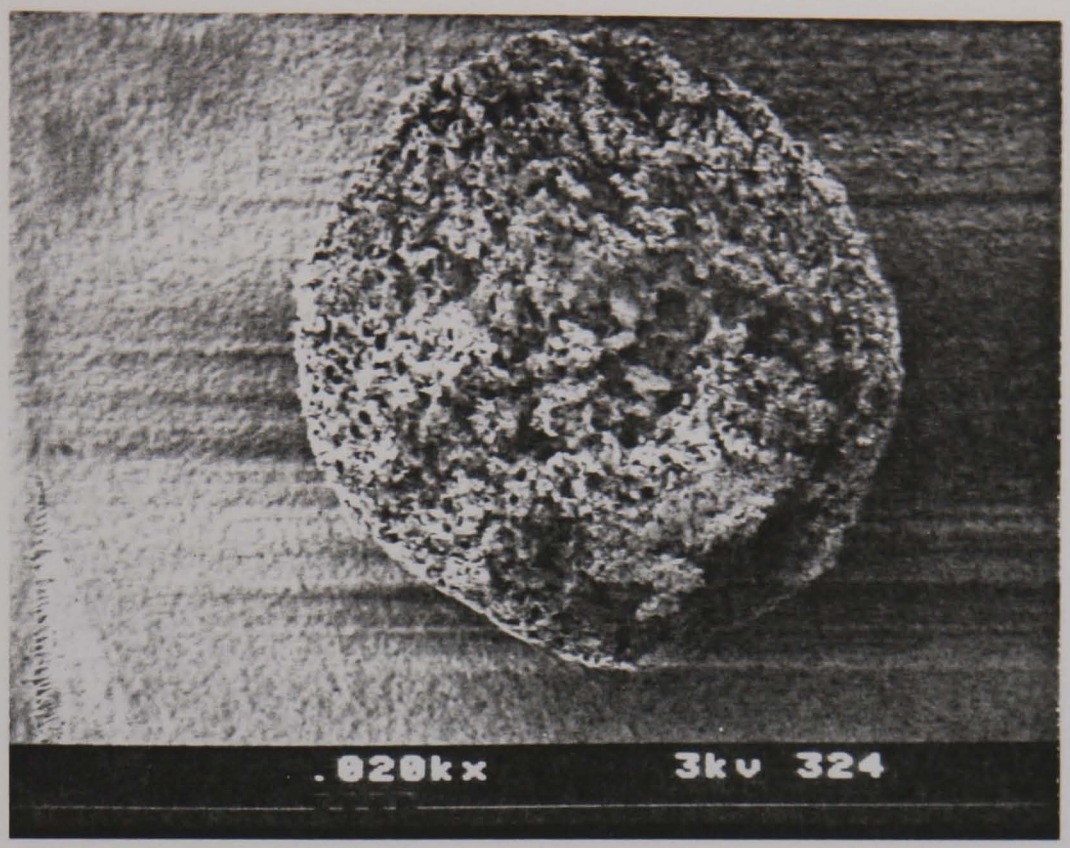


Figure 4.22a. SEM of uncoated pellet cross-section containing 80% ibuprofen (post-dissolution); x80.

Figure 4.22b. SEM of uncoated pellet cross-section containing 80% ibuprofen (post-dissolution); x400.

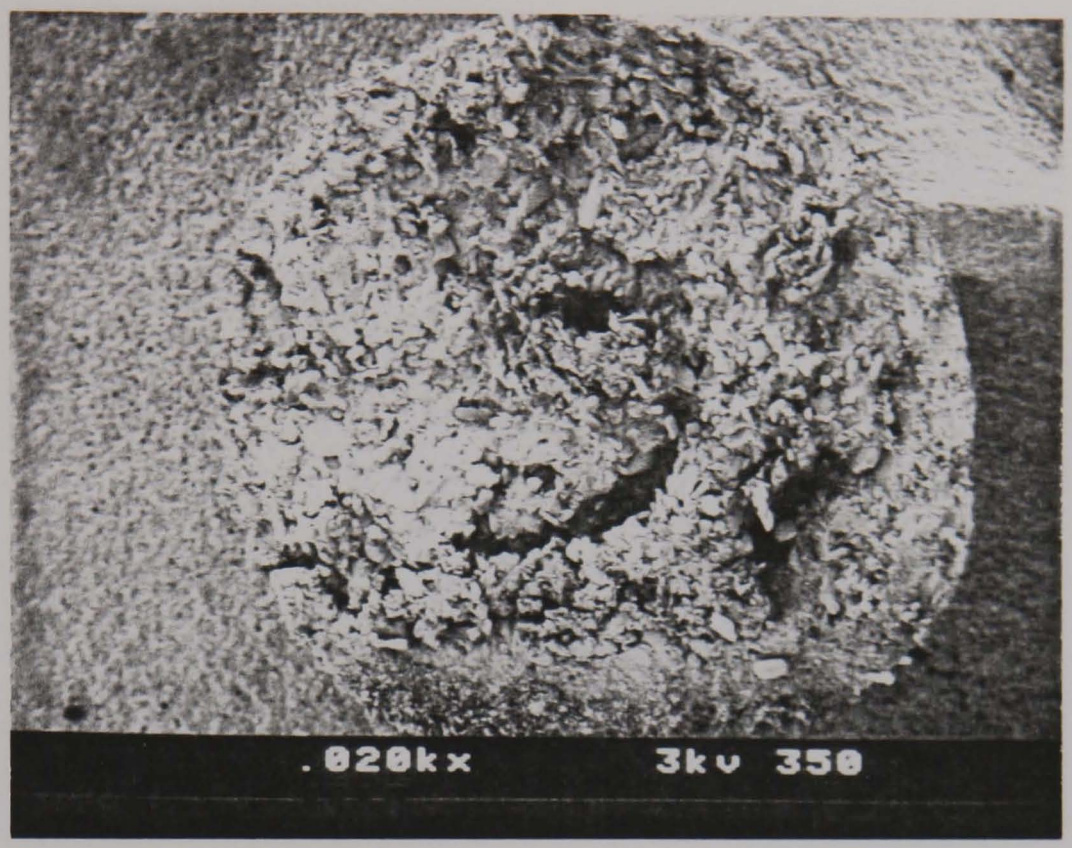


Figure 4.23a. SEM of uncoated pellet cross-section containing 60% ibuprofen (pre-dissolution); x80.

Figure 4.23b. SEM of uncoated pellet cross-section containing 60% ibuprofen (pre-dissolution); x400.

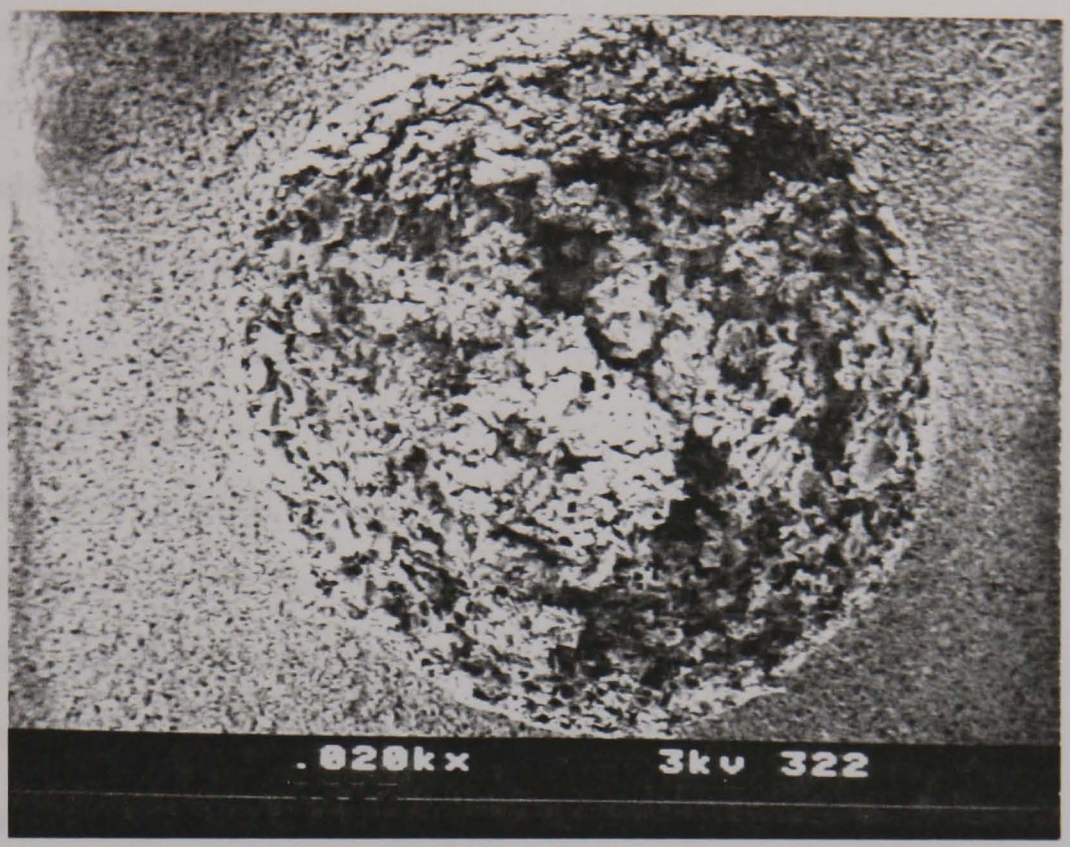


Figure 4.24a. SEM of uncoated pellet cross-section containing 60% ibuprofen (post-dissolution); x80.

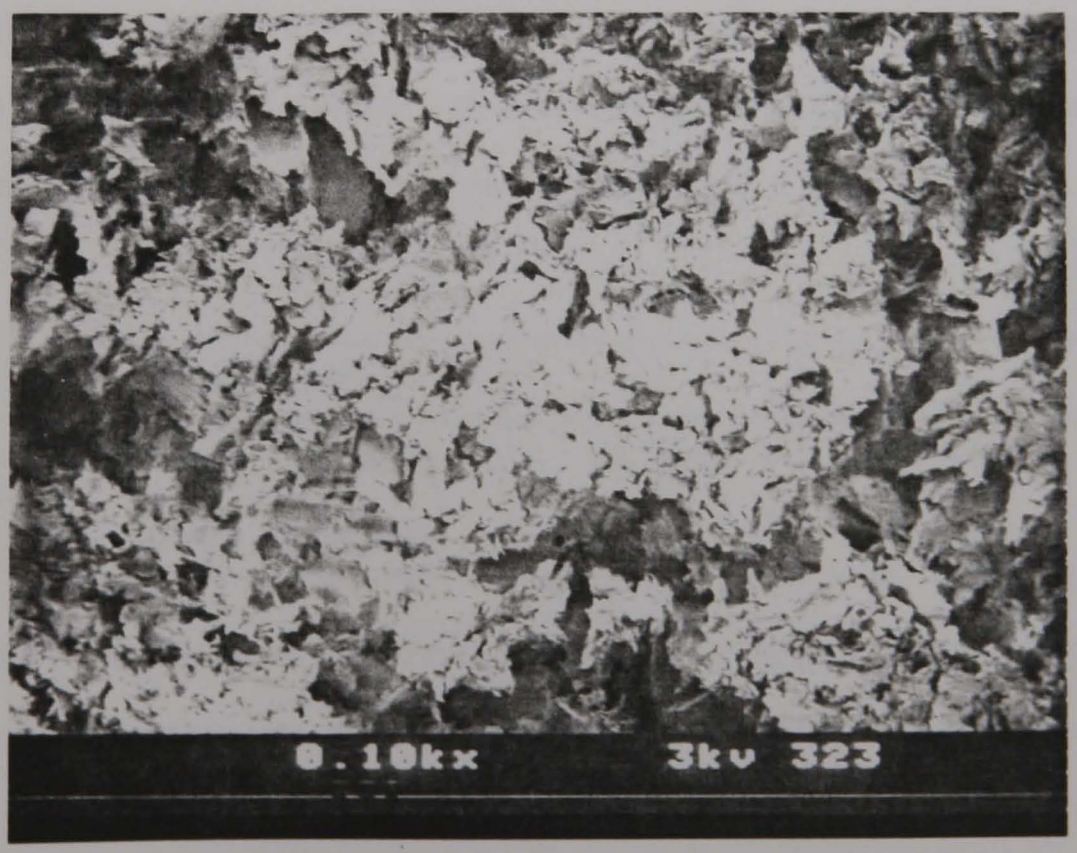


Figure 4.24b. SEM of uncoated pellet cross-section containing 60% ibuprofen (post-dissolution); x400.

As shown previously two pellet potencies are illustrated containing 80%w/w and 60%w/w drug. As with the uncoated pellet surface appearance prior to drug removal at the two drug loadings, it is not possible using this technique to differentiate between those pellets containing 80%w/w and those containing 60%w/w ibuprofen, by examining the cross-sectional appearance of these pellets (c.f. Figures 4.21 and 4.23). Comparison of the cross-sectional appearance of these drug depleted skeletal entities following dissolution testing (in terms of the initial drug loading), indicates again that the drug was fairly evenly distributed throughout the pellet matrix. Dissolution testing facilitated the creation of a pore network as a consequence of solvent penetration and the diffusion of solute molecules from the matrix. It is noteworthy that drug release from uncoated pellets containing ibuprofen is surprisingly retarded even from those pellets containing only 20%w/w microcrystalline cellulose (Table 4.1). Pellets containing 60%w/w drug exhibit a T_{90} value of just under 9 hours for example. It is postulated that whichever drug release mechanism predominates for coated pellets, drug release from uncoated pellets is diffusion controlled and exhibits first order kinetics (c.f. uncoated pellet release profiles in Figures 4.7 and 4.11).

Drug Loading	T_{50}	T_{90}
80%w/w ibuprofen	69 mins.	315 mins.
60%w/w ibuprofen	111 mins.	532 mins.

Table 4.1. Summary of *in-vitro* drug release from uncoated pellets containing ibuprofen in pH 6.8 phosphate buffer BP.

4.3.3.3. Effect of polymer type on quality and surface characteristics of film coating applied to pellets containing ibuprofen.

Figures 4.25 to 4.30 inclusive are SEMs which show the quality and surface characteristics of pellets coated with the aqueous dispersions. details of which are described in Chapter 3. Pellets coated with aqueous dispersion formulations of either Eudragit (polymethacrylate) or Surelease (ethylcellulose), exhibit satisfactory uniform smooth surface characteristics (Figures 4.25 and 4.26).

Figures 4.27 to 4.30 illustrate interesting differences in the surface characteristics of pellets coated with the aqueous Silicone Elastomer emulsion formulations; again specific formulation details and the film coating processing technique and variables are described in Chapter 3. A ratio of silicone to silica in the preparation of the emulsion of 2:1 without plasticiser (Figure 4.27) and with plasticiser (Figure 4.30), yields films of uniform, smooth surface characteristics, which at this stage of the investigation may be considered satisfactory. For ratios of silicone to silica of 4:1 and 6:1, it is evident that many surface irregularities are a feature of the resultant films. Reasons for this may be many fold and attributable to many factors. Possible explanations include poor coating processing variables, which may or may not be a causative factor. It is felt however that this is unlikely since satisfactory film quality appears to have been achieved with the 2:1 ratio. It has been concluded previously that an increase in the ratio of silicone to silica in the emulsion formulation has the effect of increasing the tendency of product sticking and agglomeration during coating. Although the capacity of the fluidising air within the coating chamber appeared to be sufficient to prevent pellet sticking and/or agglomeration during processing, it is possible that the nature of the excipients of the emulsion rendered the equilibrium conditions within the coating chamber unsuitable for these aqueous systems in some other way.

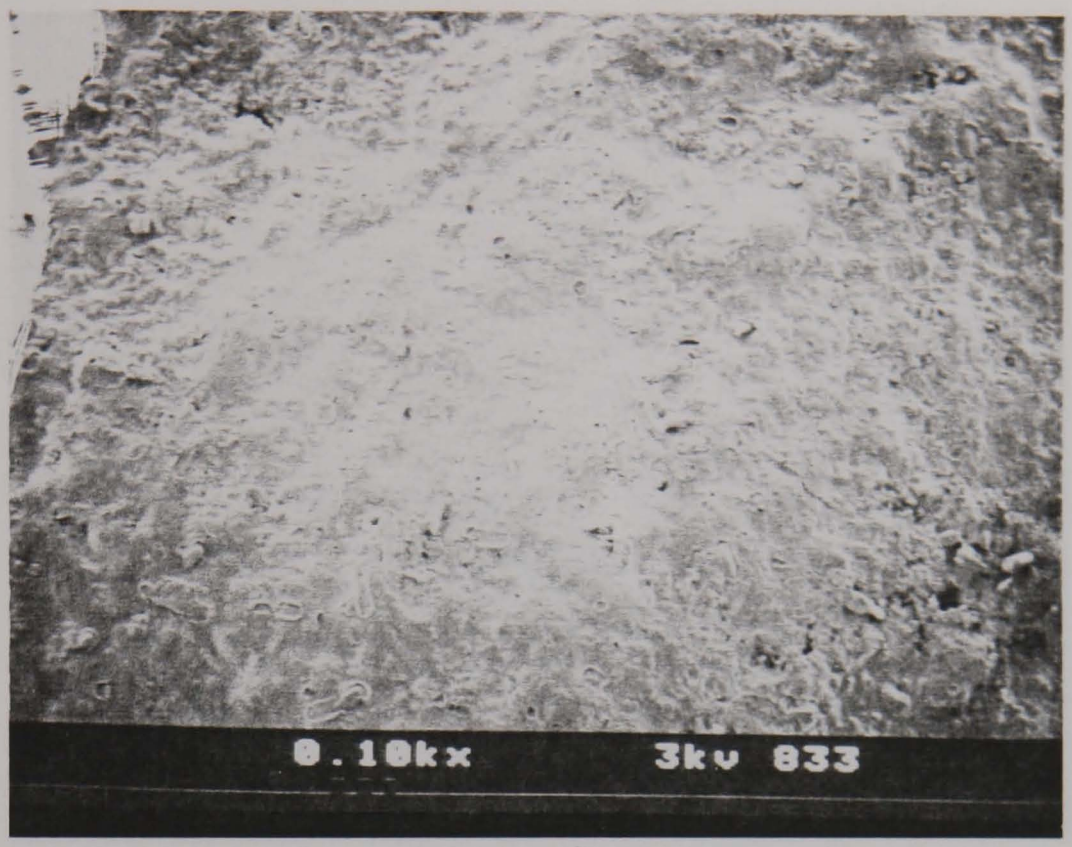


Figure 4.25. SEM of pellet surface coated with Eudragit RS/RL30D (pre-dissolution); x400.

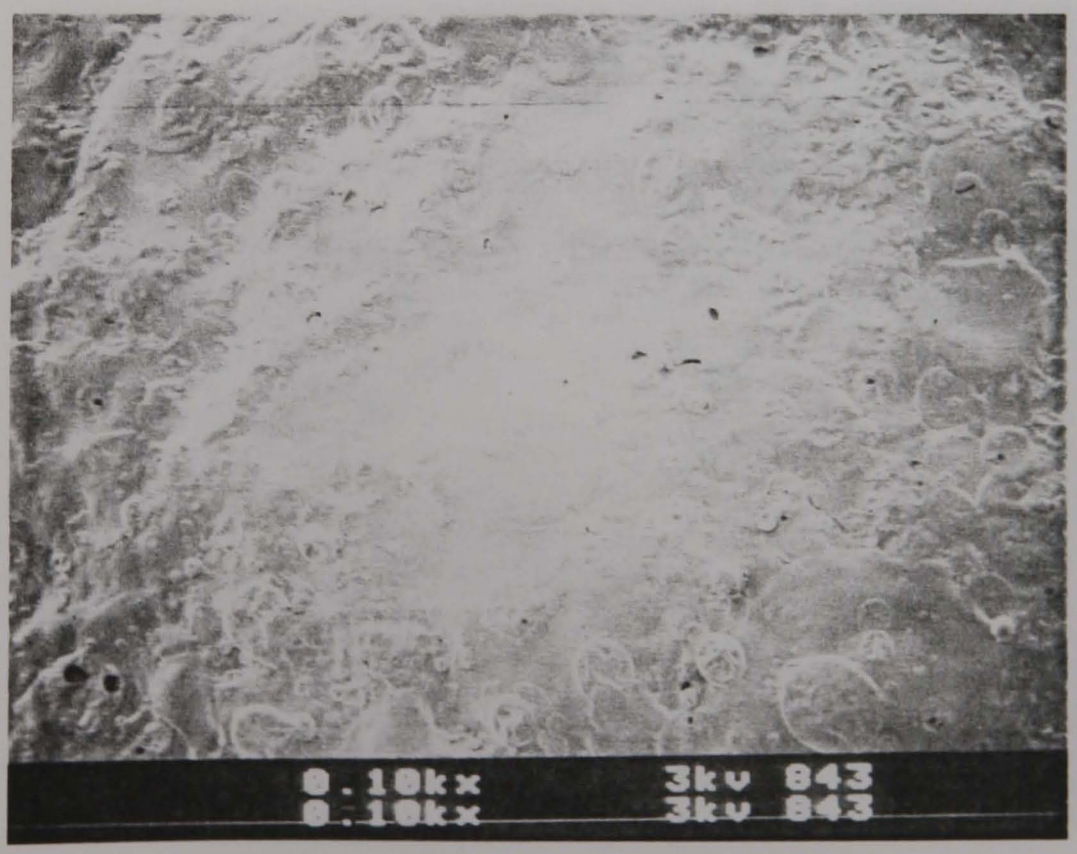


Figure 4.26. SEM of pellet surface coated with Surelease dispersion (pre-dissolution); x400.

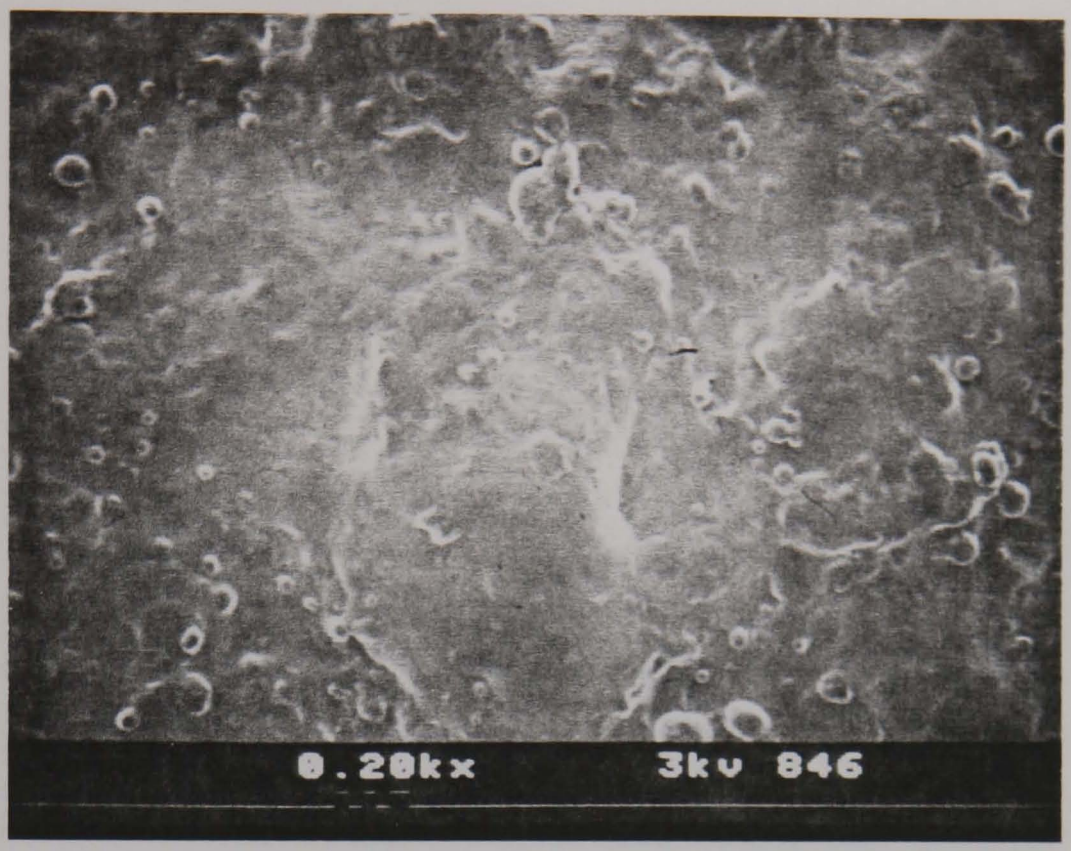


Figure 4.27. SEM of pellet surface coated with Silicone Elastomer 2:1 (pre-dissolution); x800.

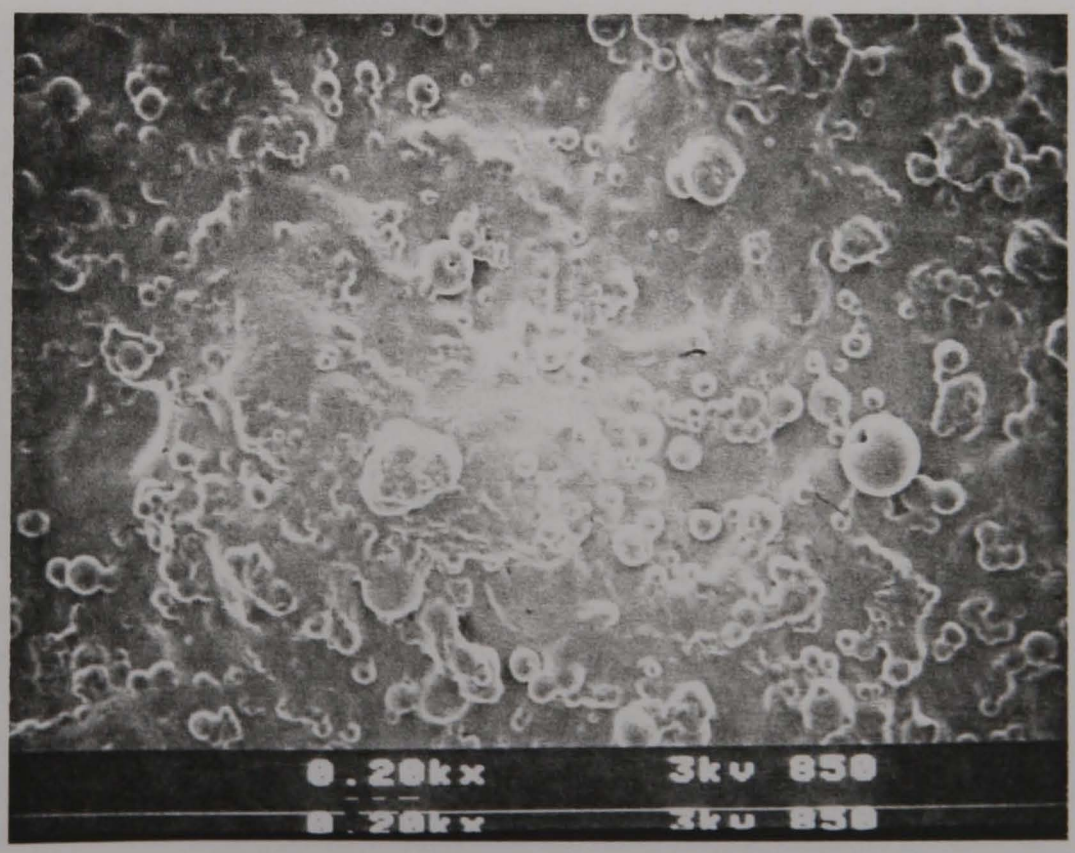


Figure 4.28. SEM of pellet surface coated with Silicone Elastomer 4:1 (pre-dissolution); x800.

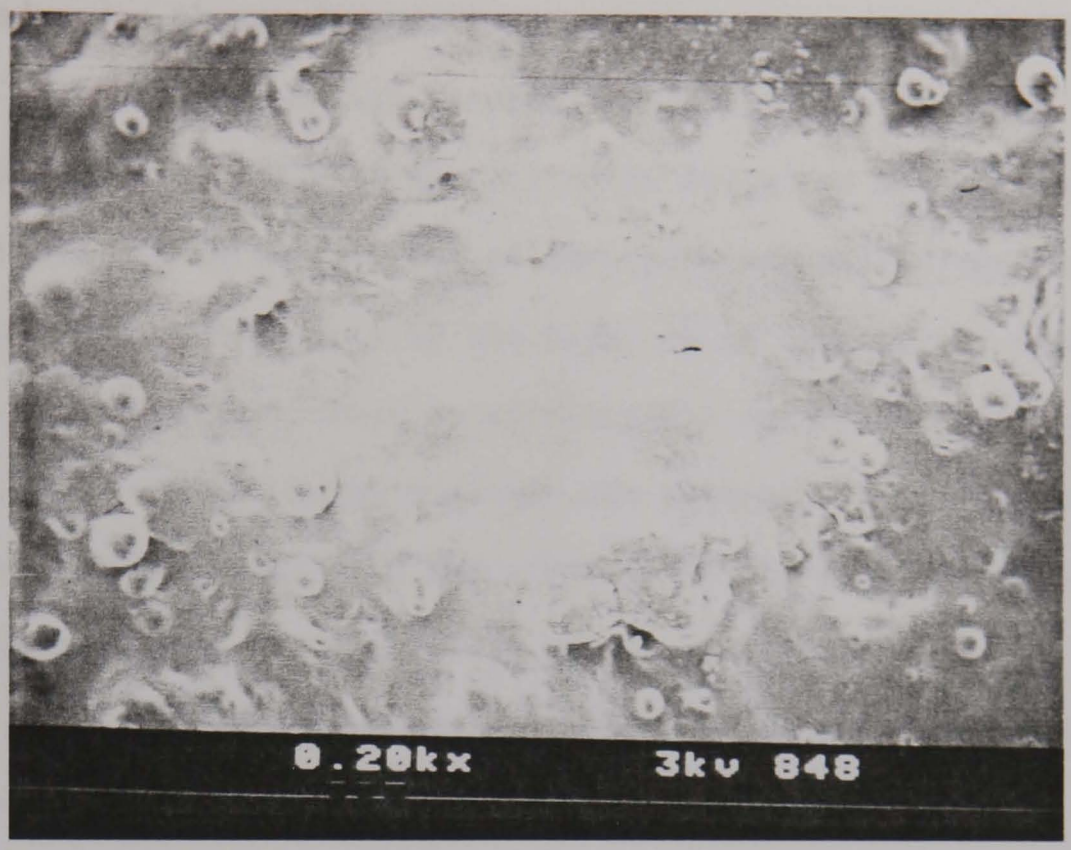


Figure 4.29. SEM of pellet surface coated with Silicone Elastomer 6:1 (pre-dissolution); x800.

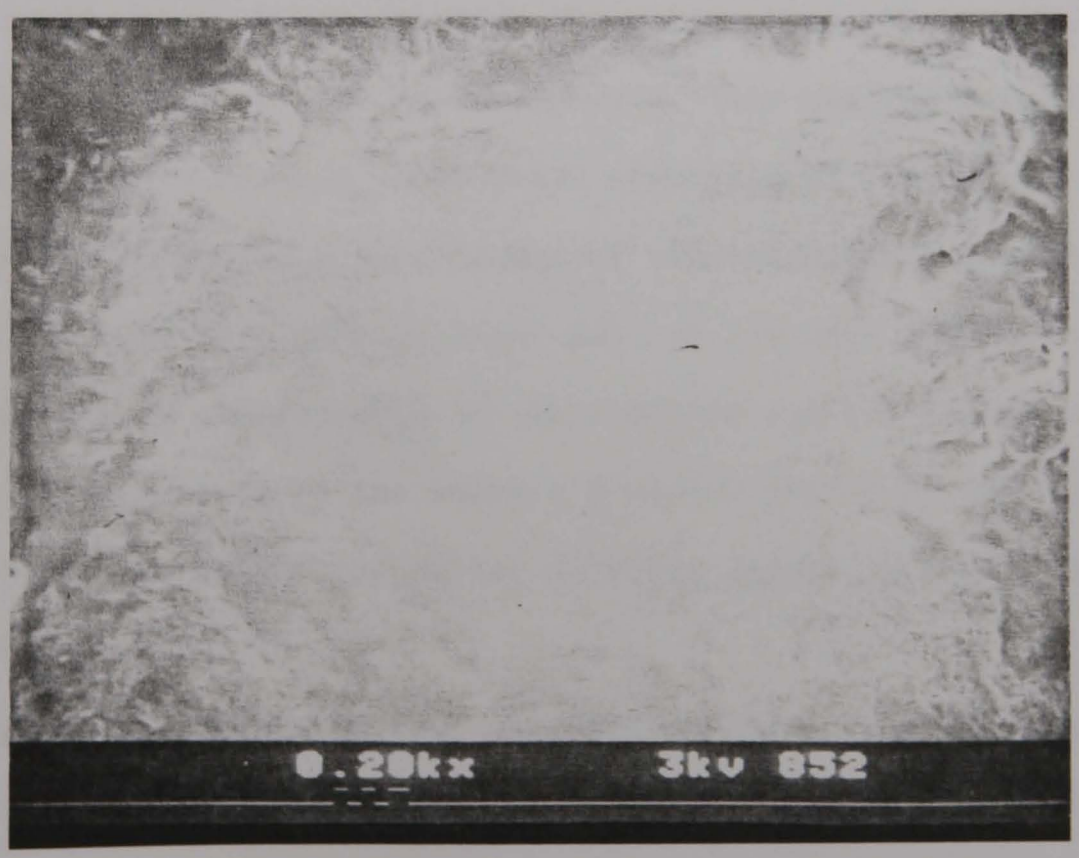


Figure 4.30. SEM of pellet surface coated with Silicone Elastomer 6:1 with 10%w/w PEG (pre-dissolution); x800.

It is possible that the rate of water removal was not necessarily optimised under these circumstances and that the quality of the film coating of those pellets illustrated in Figures 4.28 and 4.29 is somewhat impaired when compared with the 2:1 ratio (with and without incorporated plasticiser). A further effect of incorporated plasticiser, in addition to enhancing the elasticity of the film, is to enhance the rate of drug release (Figure 4.16). This is attributable to the creation of hydrophilic pores or channels within the otherwise hydrophobic polymeric membrane as a consequence of the affinity of the plasticiser for the penetrating aqueous solvent during dissolution testing.

The process involving dissolution of the plasticiser within the polymeric membrane leading to the creation of aqueous pores or channels, may or may not play a significant role in the drug release from polymer coated pellets containing ibuprofen. Figure 4.16 enables confirmation of the drug release enhancing properties of incorporated plasticiser and illustrates that these pores or channels do have a role in facilitating diffusion of solute molecules from the pellet core into the bulk solution. The drug release mechanism from those pellets coated with the silicone emulsion formulation without incorporated plasticiser is membrane controlled as a consequence of the hydrophobic nature of this film. It is possible that at least part of the rate controlling mechanism may be attributable to the relative osmotic pressures, in respect of difference in the osmotic pressure caused by the presence of solute molecules within the pellet core and solute concentration within the bulk solvent.

Figure 4.16 indicates that drug release from those coated pellets without incorporated plasticiser exhibits first order kinetics. The creation of plasticiser pores within the membrane for those pellets coated with silicone emulsion 2:1 with the addition of polyethylene glycol, appears initially to display first order kinetics, but the rate

controlling mechanism appears to become zero order as the latter 25% of drug is leached from the pellet core.

It may be concluded that the presence of hydrophilic pores within an otherwise hydrophobic membrane, does contribute to drug release from pellets. It would appear however that the major release controlling mechanism is not due to the presence of plasticiser pores, but largely by the diffusional transport of solute molecules across the polymeric membrane and possibly the relative osmotic pressure within the pellet core and the bulk dissolution medium.

4.3.3.4. Effect of polymer type on the surface characteristics of film coating applied to pellets containing ibuprofen, following drug removal.

Figures 4.31 to 4.36 are SEMs which show the surface characteristics of pellets which have been coated with the various polymers after drug removal.

The polymethacrylate film contained the plasticiser triethylcitrate. This was necessary to reduce the glass transition temperature of the polymer thus ensuring polymer coalescence and complete film formation during the coating process; it also improves the elastic properties of the film. Thus a water soluble component is incorporated into an otherwise aqueous insoluble polymeric membrane. It is not unreasonable to expect the plasticiser to dissolve in the aqueous phase resulting in the creation of pores within the film coat. Figures 4.31a and 4.31b demonstrate this phenomena exceptionally well. The integrity of the film has been compromised by the removal of plasticiser from the membrane into the bulk solution. This has the consequence of at least contributing to drug release from the pellet core; these figures show the exposed core of the pellet where the integrity of the polymeric film has been compromised as a consequence of plasticiser removal by dissolution testing.

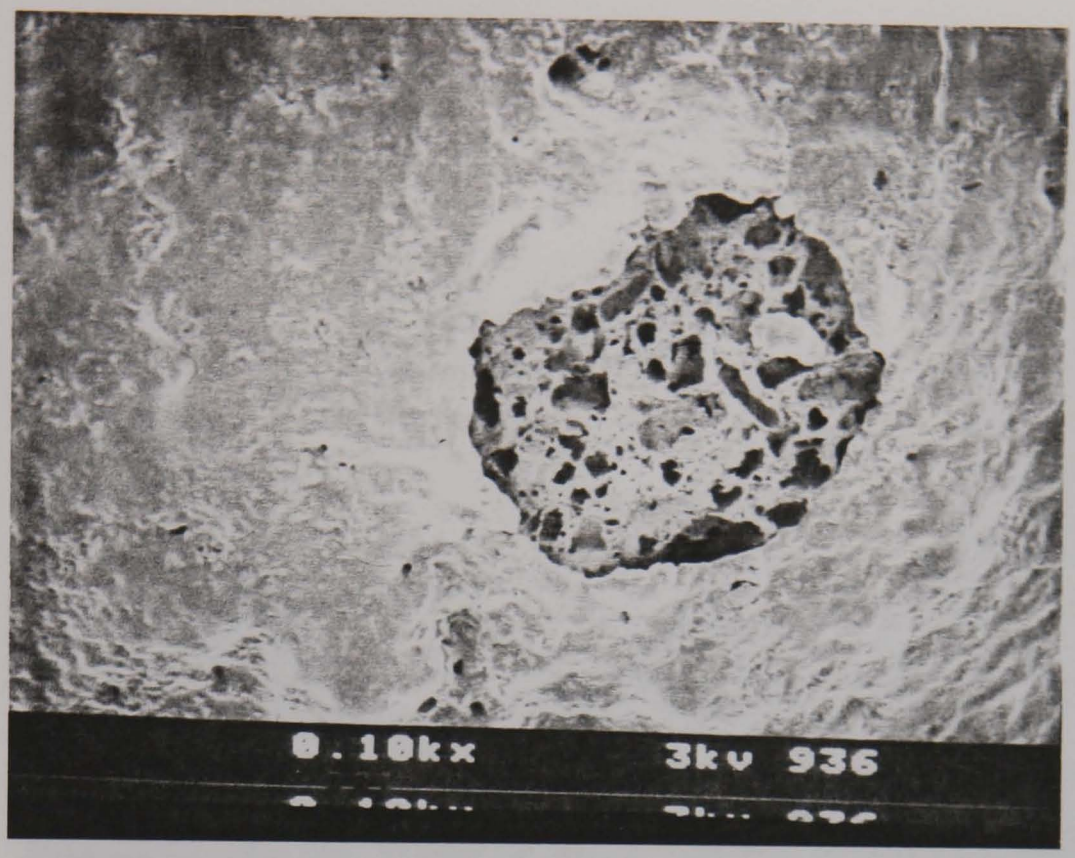


Figure 4.31a. SEM of pellet surface coated with Eudragit RS/RL30D (post-dissolution); x400.

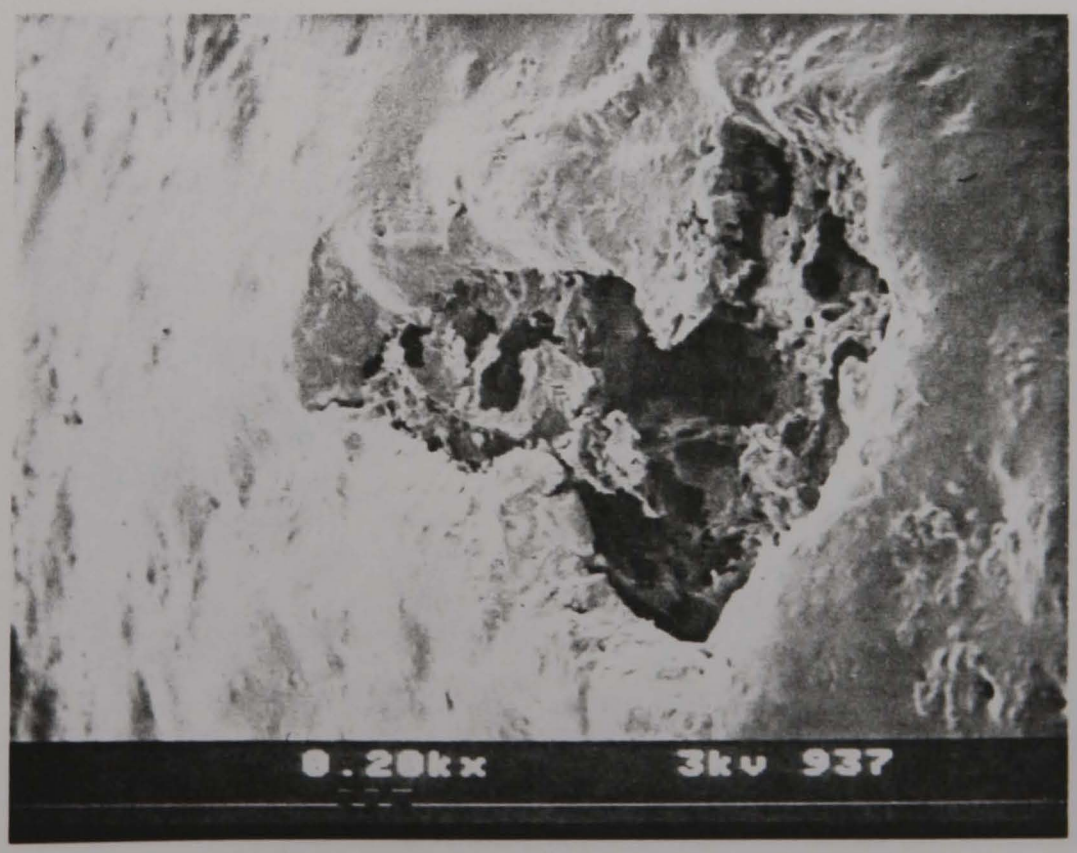


Figure 4.31b. SEM of pellet surface coated with Eudragit RS/RL30D (post-dissolution); x800.

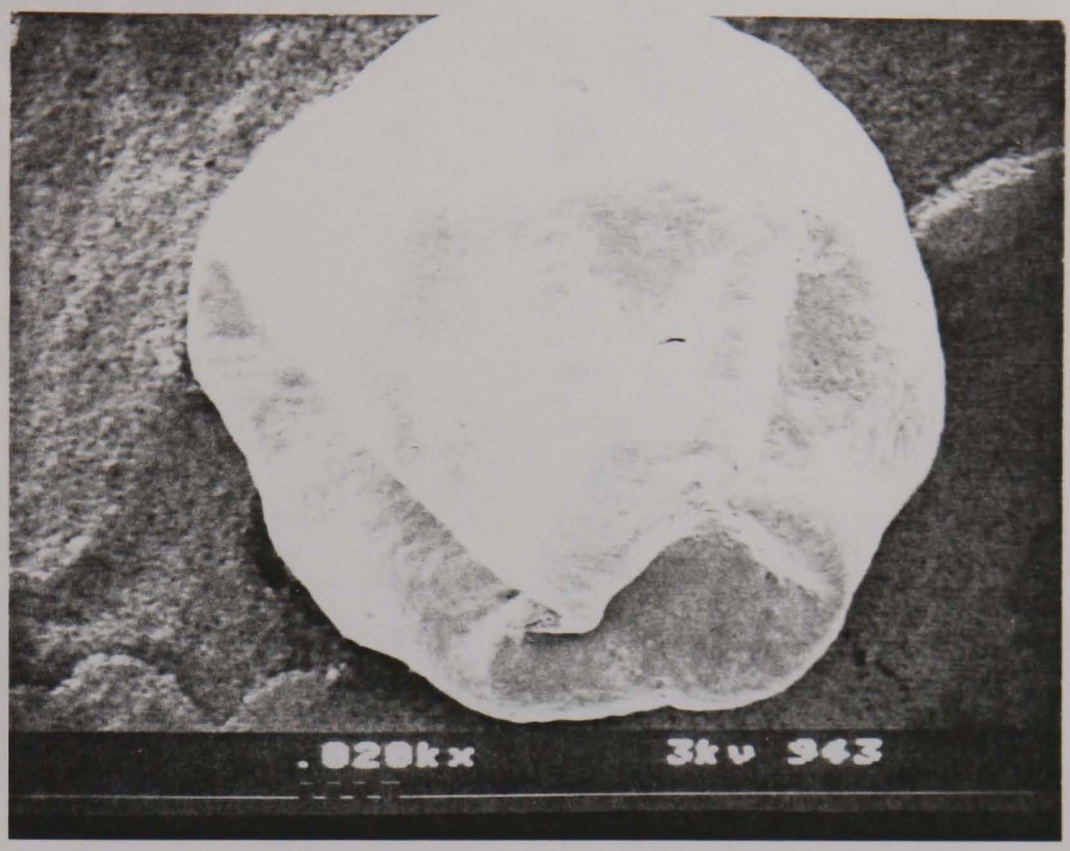


Figure 4.32a. SEM of pellet surface coated with Surelease dispersion (post-dissolution); x80.

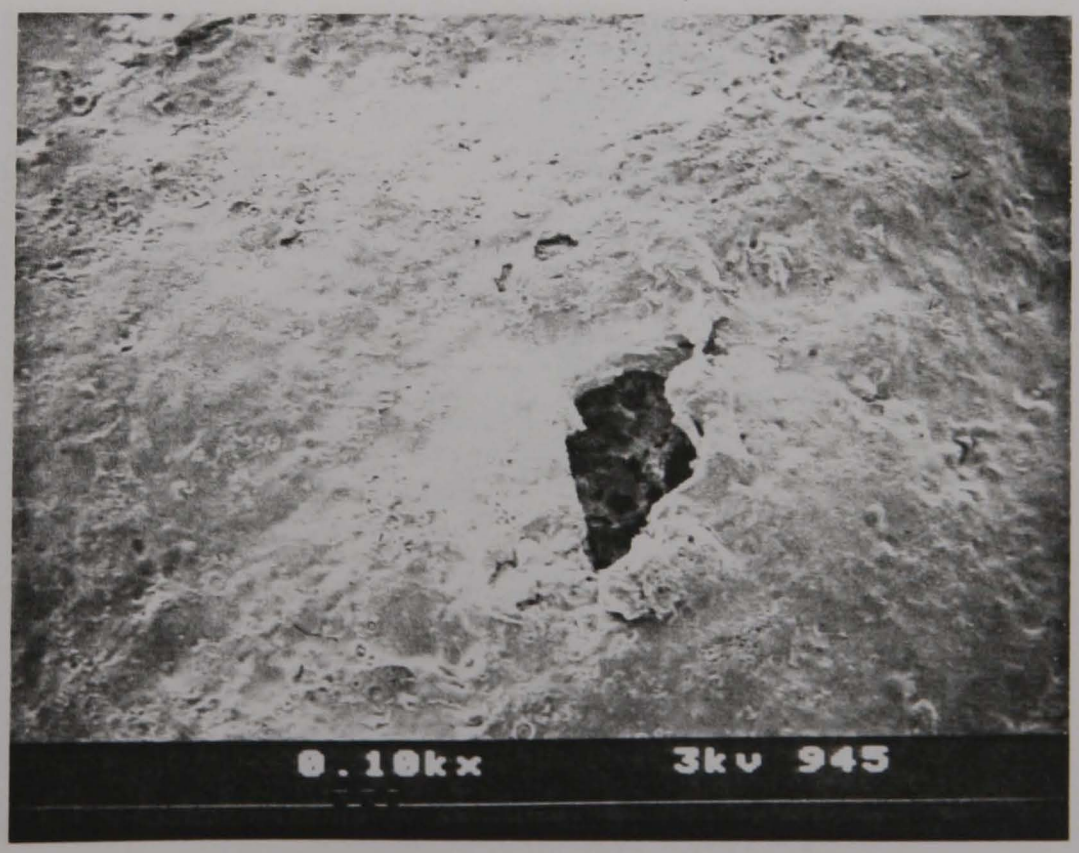


Figure 4.32b. SEM of pellet surface coated with Surelease dispersion (post-dissolution); x400.

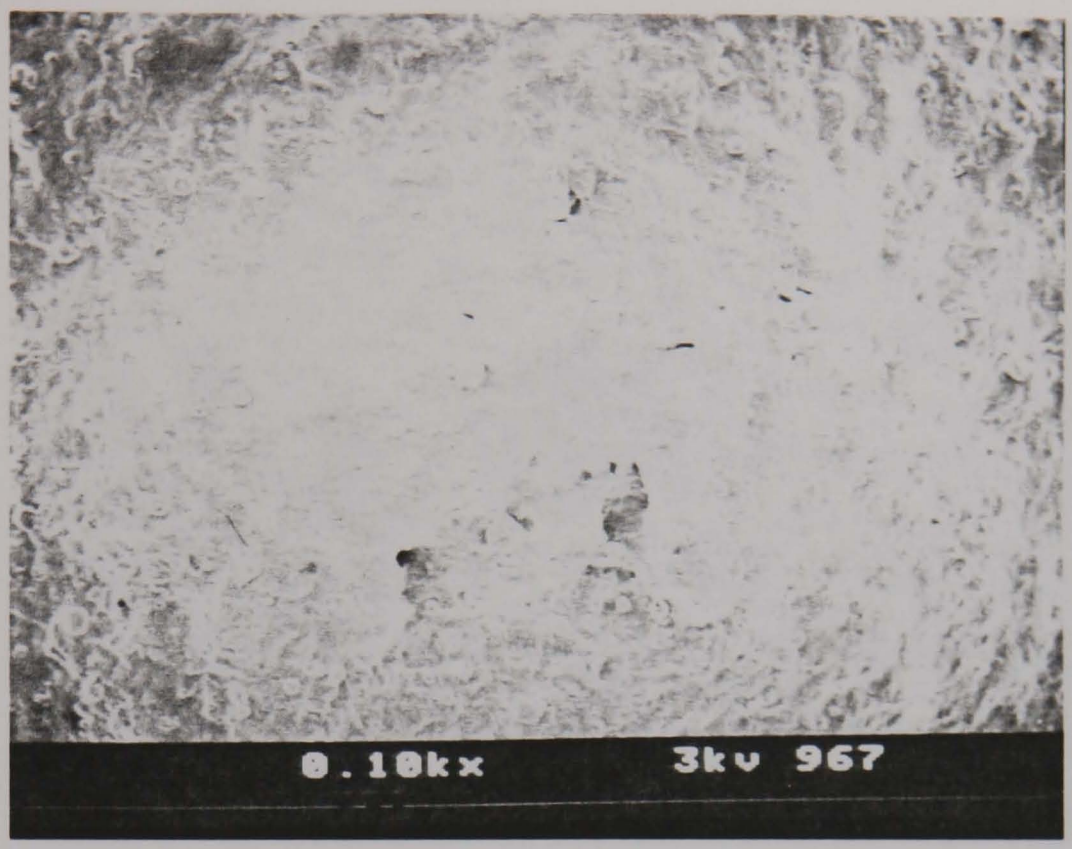


Figure 4.33a. SEM of pellet surface coated with Silicone Elastomer 2:1 (post-dissolution); x400.

Figure 4.33b. SEM of pellet surface coated with Silicone Elastomer 2:1 (post-dissolution); x800.

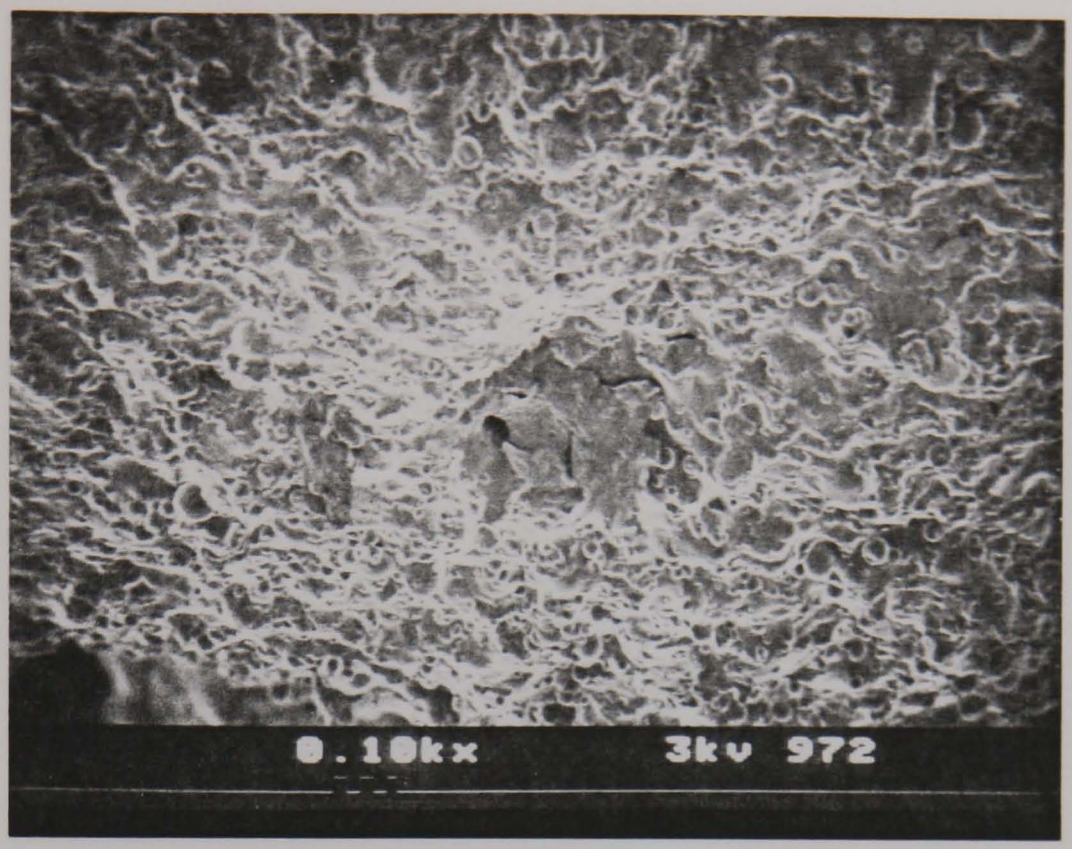


Figure 4.34a. SEM of pellet surface coated with Silicone Elastomer 4:1 (post-dissolution); x400.

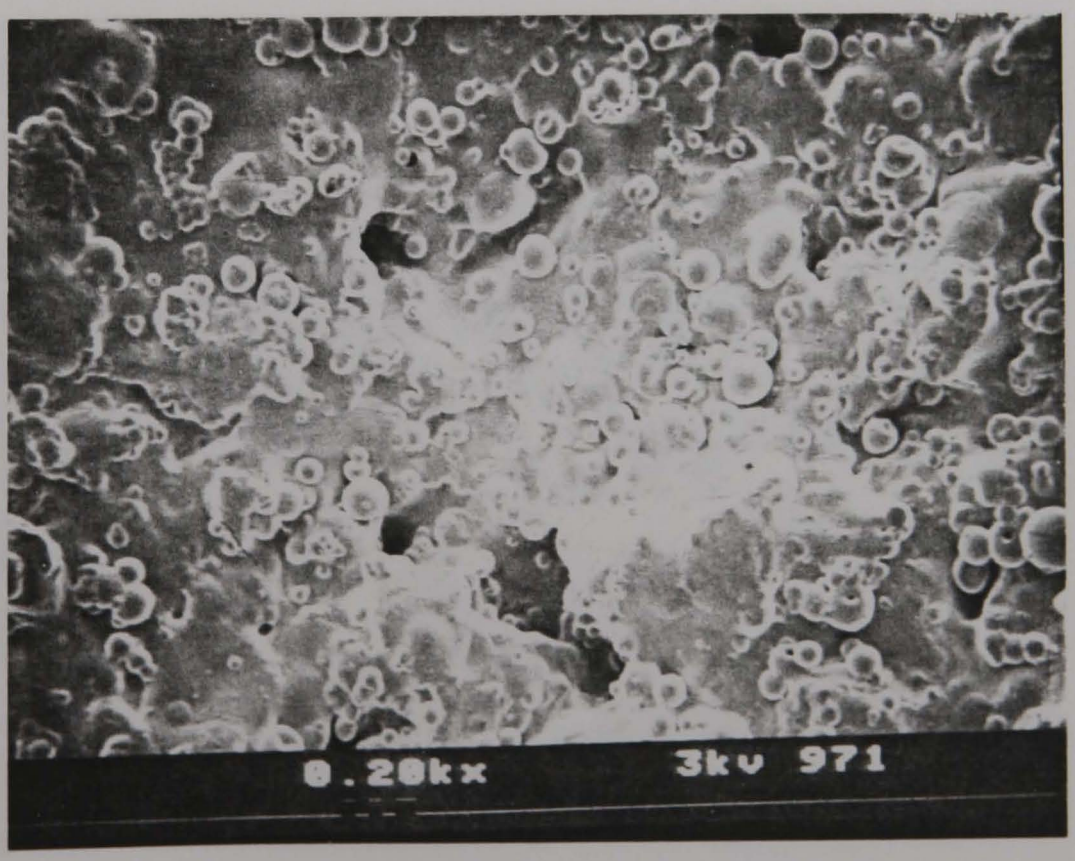


Figure 4.34b. SEM of pellet surface coated with Silicone Elastomer 4:1 (post-dissolution); x800.

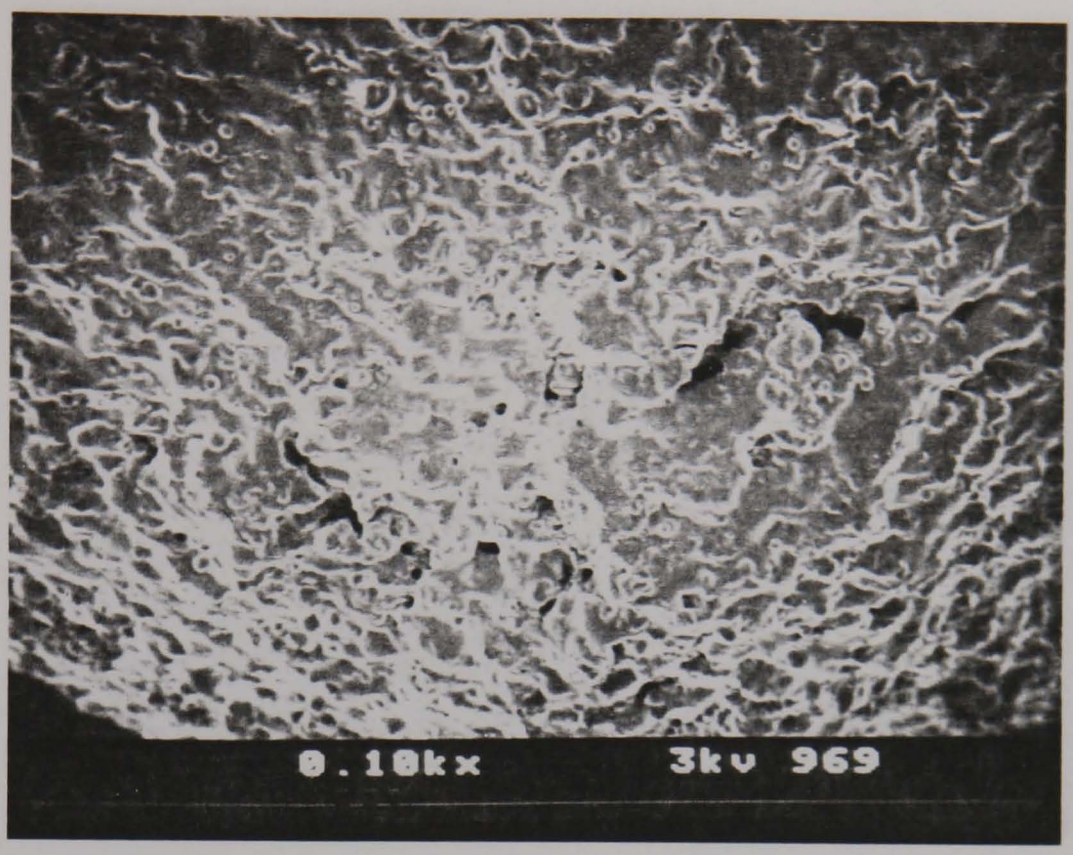


Figure 4.35a. SEM of pellet surface coated with Silicone Elastomer 6:1 (post-dissolution); x400.

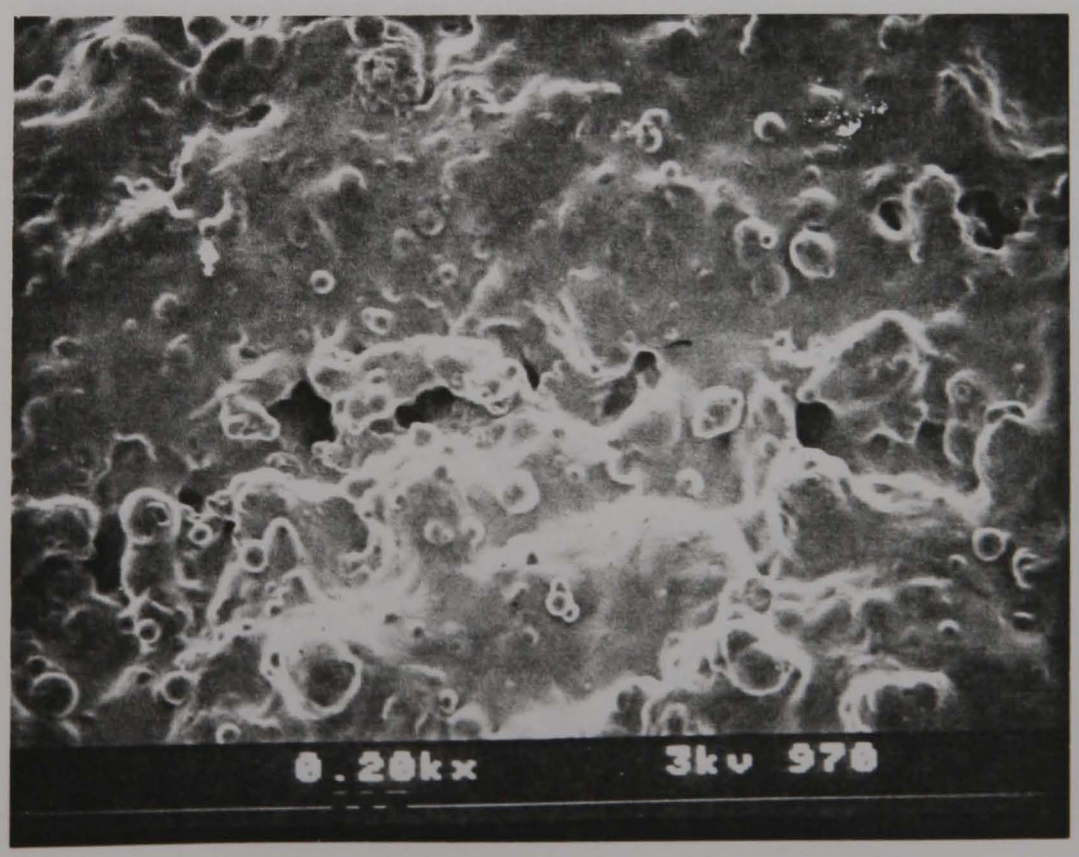


Figure 4.35b. SEM of pellet surface coated with Silicone Elastomer 6:1 (post-dissolution); x800.

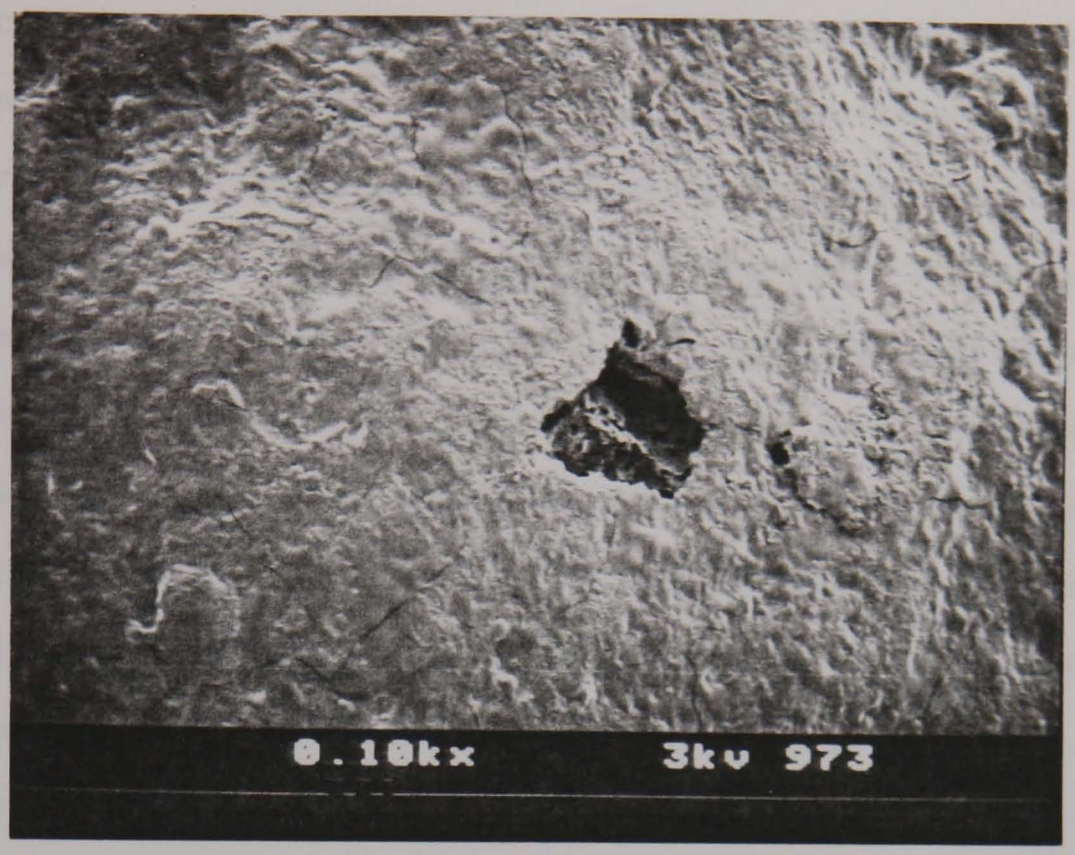


Figure 4.36a. SEM of pellet surface coated with Silicone Elastomer 2:1 with 10%w/w PEG (post-dissolution); x400.

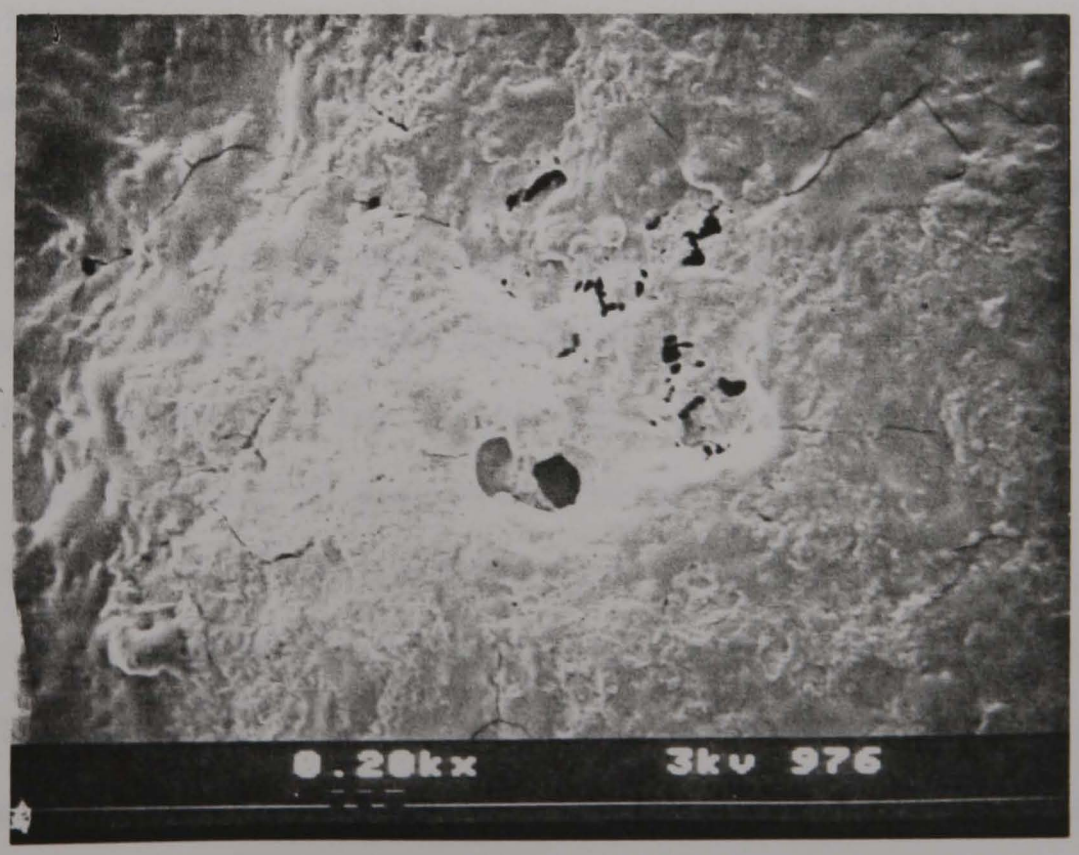


Figure 4.36b. SEM of pellet surface coated with Silicone Elastomer 2:1 with 10%w/w PEG (post-dissolution); x800.

The skeletal network of drug depleted cores containing only microcrystalline cellulose are exposed; the core formulation in this case initially contained 30% microcrystalline cellulose and 70%w/w ibuprofen. The incorporation of plasticiser into aqueous dispersions containing the polymethacrylates was necessary for film formation. It was therefore not possible to prepare coated pellets using the same formulation without plasticiser. There are therefore no comparative release profiles available for pellets coated with the polymethacrylate dispersion without added plasticiser, as there are for the silicone coated particles. It is postulated that although solute transport through aqueous pores within the otherwise hydrophobic membrane contributes to drug release, it is not necessarily the main mechanism of drug removal from the pellet core.

Figures 4.32a and 4.32b show the surface of a drug depleted pellet coated with a commercial ethylcellulose formulation (Surelease) containing plasticiser; details relating to the formulation of the Surelease formulation have been given previously (section 3.2.2). Figure 4.32a illustrates how the film coat envelopes the pellet which initially contained 80%w/w ibuprofen; some pellet shrinkage is apparent. This may be attributable to core shrinkage as a consequence of drug removal and the drying out of the pellet after dissolution testing. As previously mentioned, pellets were dried under ambient conditions of humidity and temperature in order to try and minimise core shrinkage due to drug removal and increased voidage within pellet cores.

Alternatively, it is possible that the relative osmotic pressures between the solute concentration in the coated pellet core and in the bulk solution during *in-vitro* testing, caused a degree of swelling of the pellet with a resultant "expanding" or "stretching" of the film coat, which was unrecoverable after drug removal and subsequent drying of the coated pellet. This effect has not been seen with the other coating systems studied.

Figure 4.32b shows the creation of pores within the film coat as a result of *in-vitro* testing. Again the pellet core is exposed and it is postulated that the leaching of drug from the core through these pores or cracks only plays a contributory part in the release of drug and that it is not the predominating mechanism; this is on account of the frequency of these craters.

Figures 4.33 to 4.36 inclusive illustrate the nature of the polymeric film following drug removal by dissolution testing. It is apparent that breach of the film resulting in exposed core for those pellets coated with an unplasticised Silicone Elastomer membrane, is not occurring to anywhere near the extent of those plasticised films discussed previously (Figures 4.33, 4.34 and 4.35 inclusive). The proposed mechanism of drug release from these entities is by diffusion of solute molecules across the polymeric membrane, with a possibility of the process of osmosis contributing the release mechanism. Even under a magnification of x800 exposed core is not evident following complete drug removal. This is as expected since these films are exceptionally hydrophobic and there is no incorporated plasticiser ensuring the creation of pores within the film.

Figure 4.36 shows that the presence of plasticiser within a silicone elastomer membrane (as a result of contact with an aqueous solvent), will cause the formation of aqueous pores as the hydrophilic plasticiser is leached from the otherwise hydrophobic film by the penetrating aqueous phase. The extent of this process is obviously totally dependent upon the concentration of plasticiser within the aqueous silicone emulsion. This factor may not be used as a means of controlling drug release from this polymer however, since increasing polyethylene glycol content leads to product sticking and agglomeration during the film coating process. It is anticipated that the presence of plasticiser does not have a major effect on the drug release mechanism from pellets coated with these silicone formulations.

4.3.3.5. Effect of polymer type on the cross-sectional characteristics of film coated pellets containing ibuprofen following drug removal.

Figures 4.37 to 4.42 inclusive show sectioned drug depleted pellets. It is possible to differentiate between the skeletal structure of the microcrystalline cellulose core remaining after drug removal by *in-vitro* dissolution and the polymeric membrane surrounding the core in each of the pellets illustrated at the relatively low magnification of x80. Figures 4.39a, 4.40a, 4.41a and 4.42a clearly show that at silicone to silica ratios of 4:1 and 6:1 in particular, there appears to be poor adhesion/cohesion between the pellet core and the film coat. It appears with these formulations that the film coat has a tendency to become detached from the pellet core. At a ratio of silicone to silica of 2:1 (Figure 4.39a) film detachment is evident. However incorporation of polyethylene glycol into the film formulation appears at worst, to reduce this poor adhesion between these two components.

All pellets illustrated which are coated with the Silicone Elastomer formulations contained 80%w/w ibuprofen in the core formulation prior to *in-vitro* dissolution testing.

Poor adhesion of the Silicone Elastomer films to pellet cores is not the only problem associated with the use of this product as a means of achieving a release retarding film coating for multiparticulates. Already discussed in detail is the tendency for product sticking and agglomeration during the coating process with these systems. Discussed subsequently in Chapter 7, is the fact that it was not possible to compact pellets coated with silicone formulations into tablets, due to these pellets exhibiting instant recovery on removal of the applied load associated with the compression process; it was not physically possible to form a tablet containing Silicone Elastomer coated pellets.

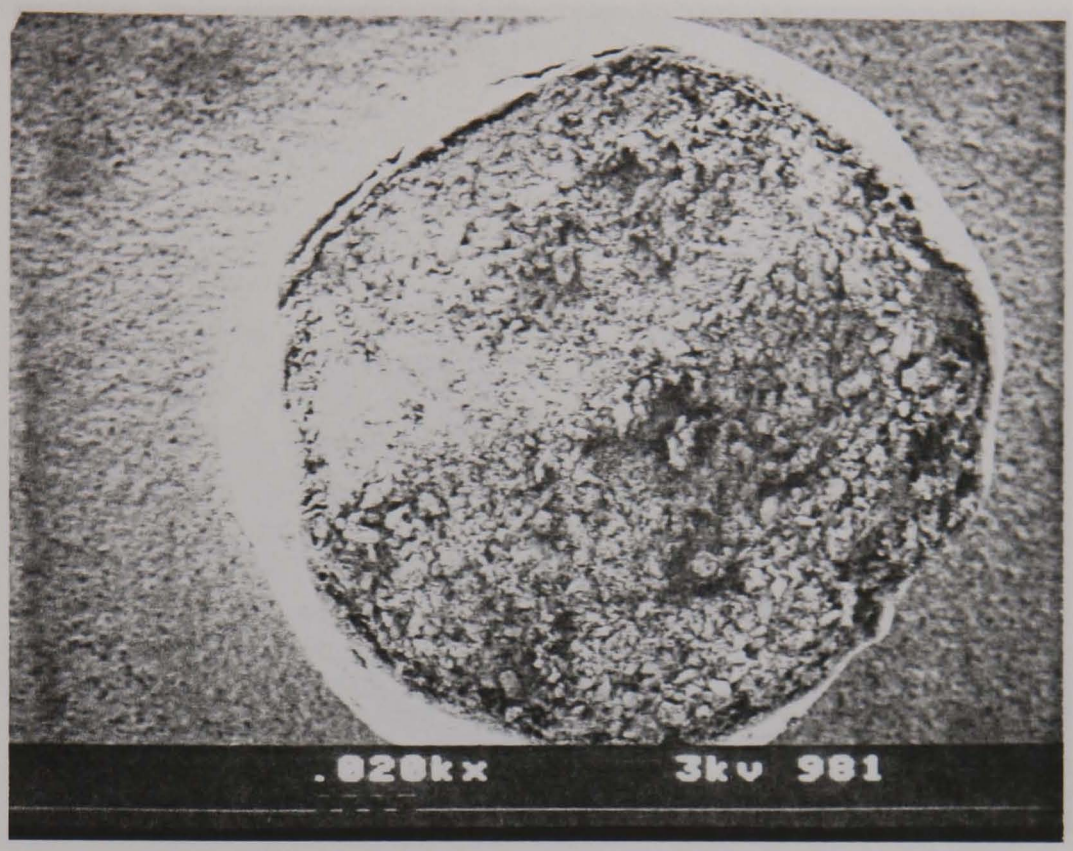


Figure 4.37a. SEM of pellet cross-section coated with Eudragit RS/RL30D (post-dissolution); 80% drug; x80.

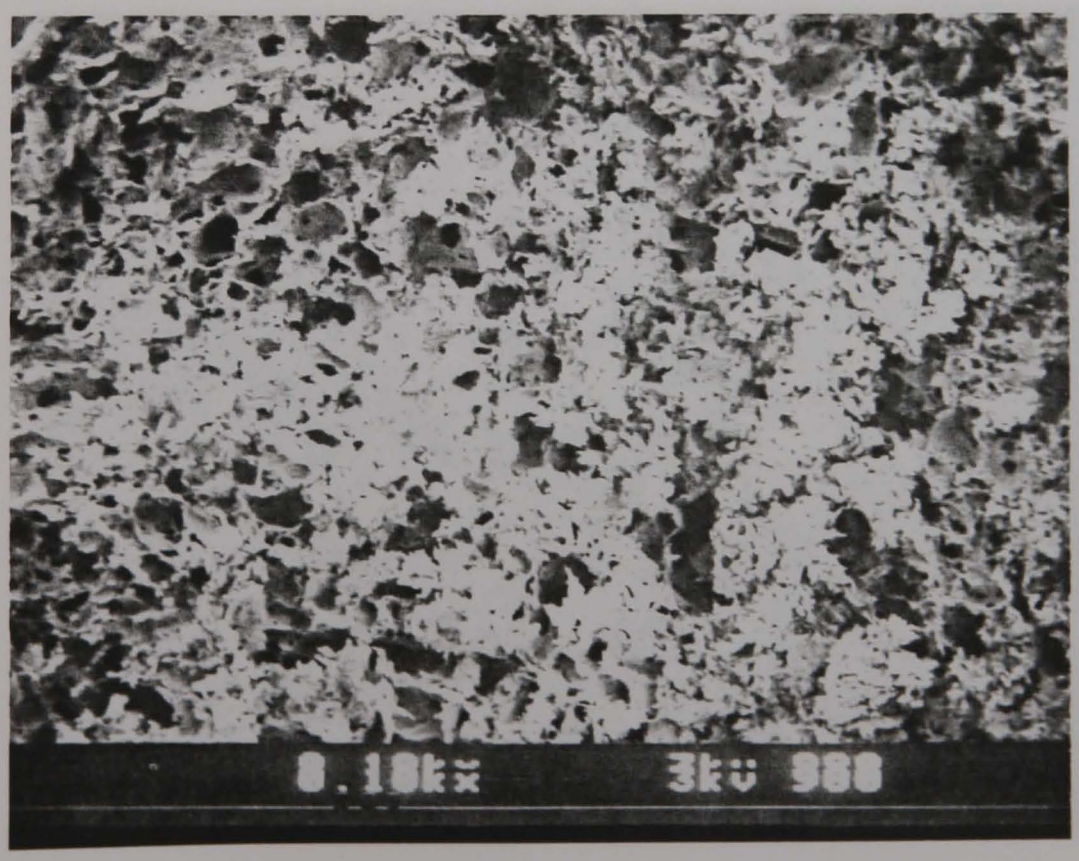


Figure 4.37b. SEM of pellet cross-section coated with Eudragit RS/RL30D (post-dissolution); 80% drug; x400.

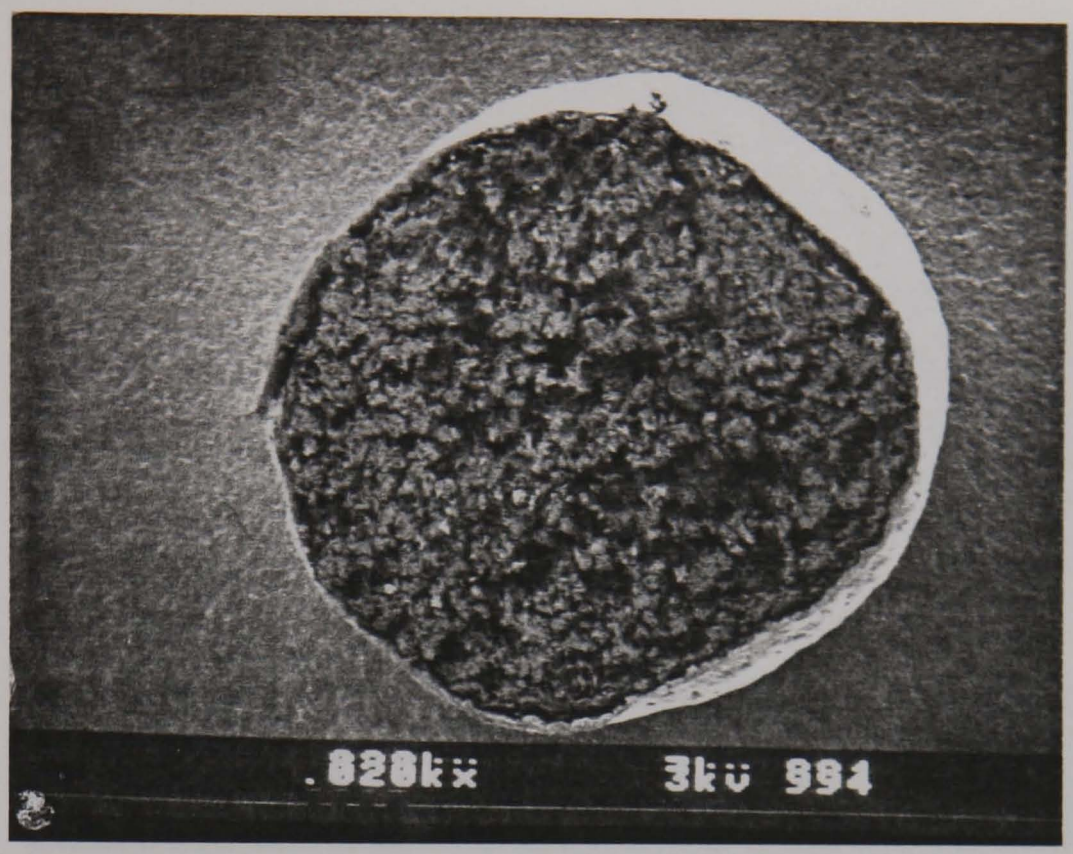


Figure 4.38a. SEM of pellet cross-section coated with Surelease dispersion (post-dissolution); 80% drug; x80.

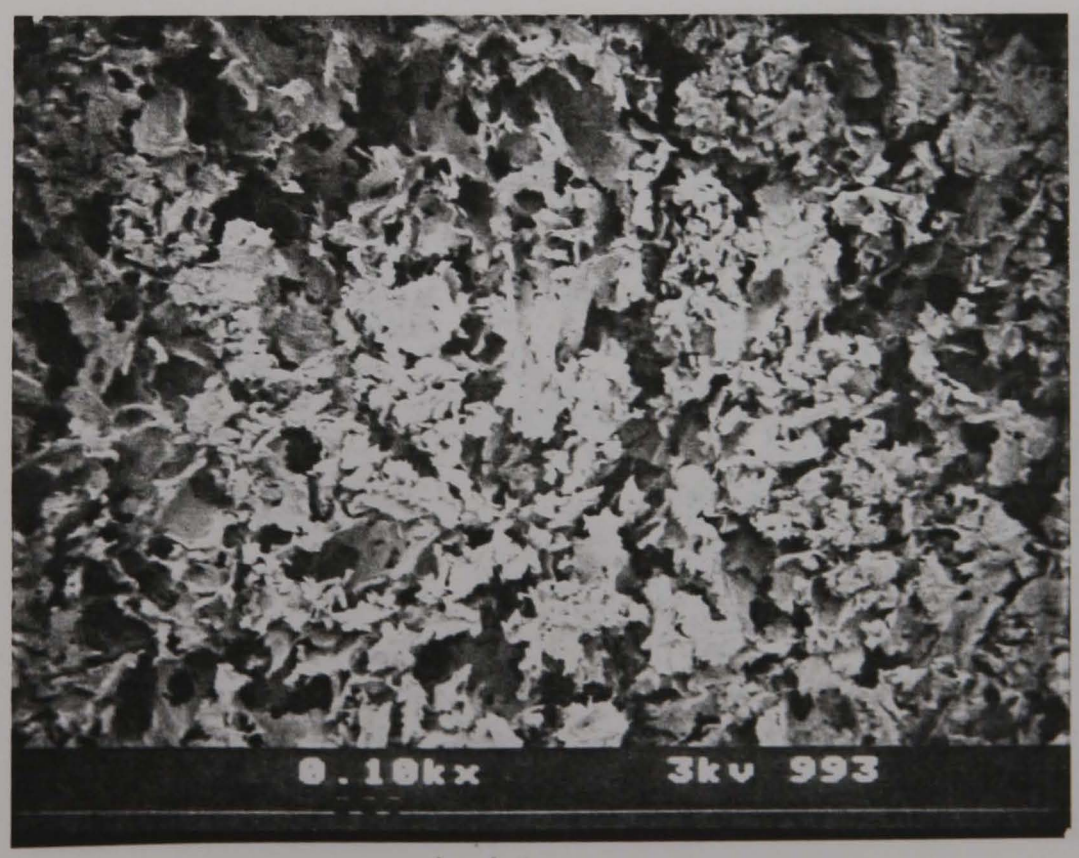


Figure 4.38b. SEM of pellet cross-section coated with Surelease dispersion (post-dissolution); 80% drug; x400.

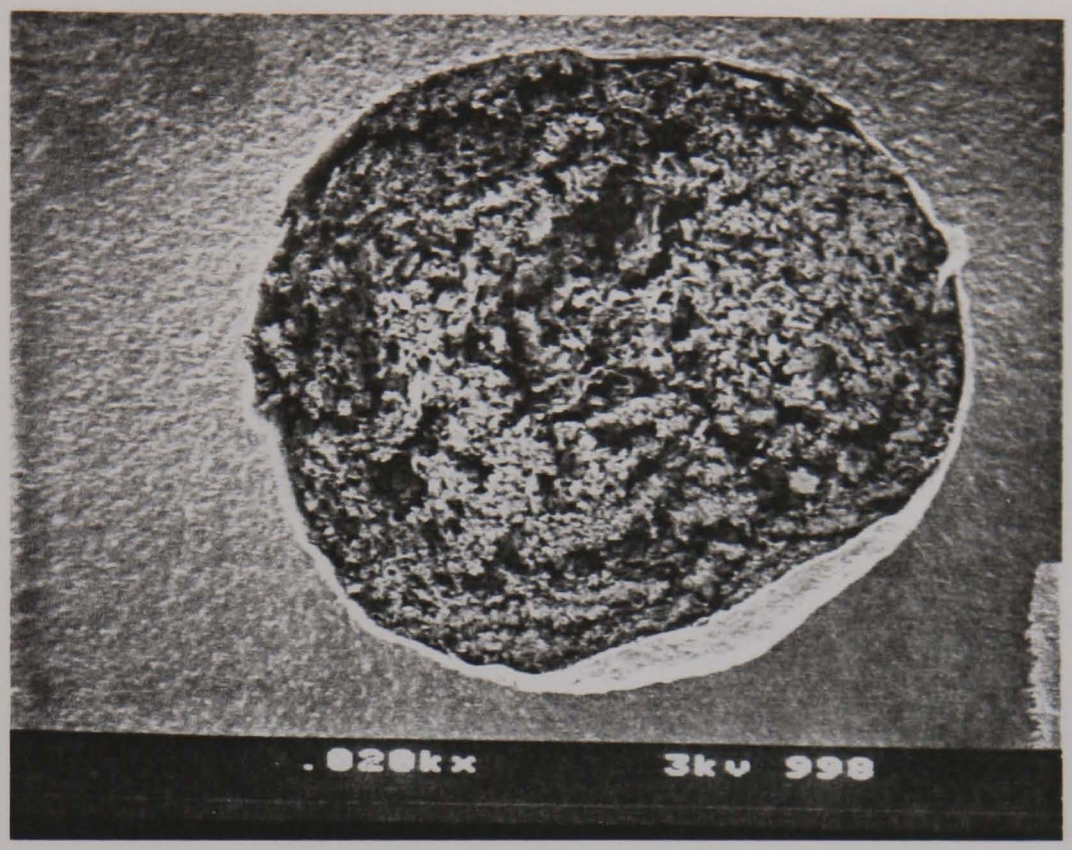


Figure 4.39a. SEM of pellet cross-section coated with Silicone Elastomer 2:1 (post-dissolution); x80.

Figure 4.39b. SEM of pellet cross-section coated with Silicone Elastomer 2:1 (post-dissolution); x400.

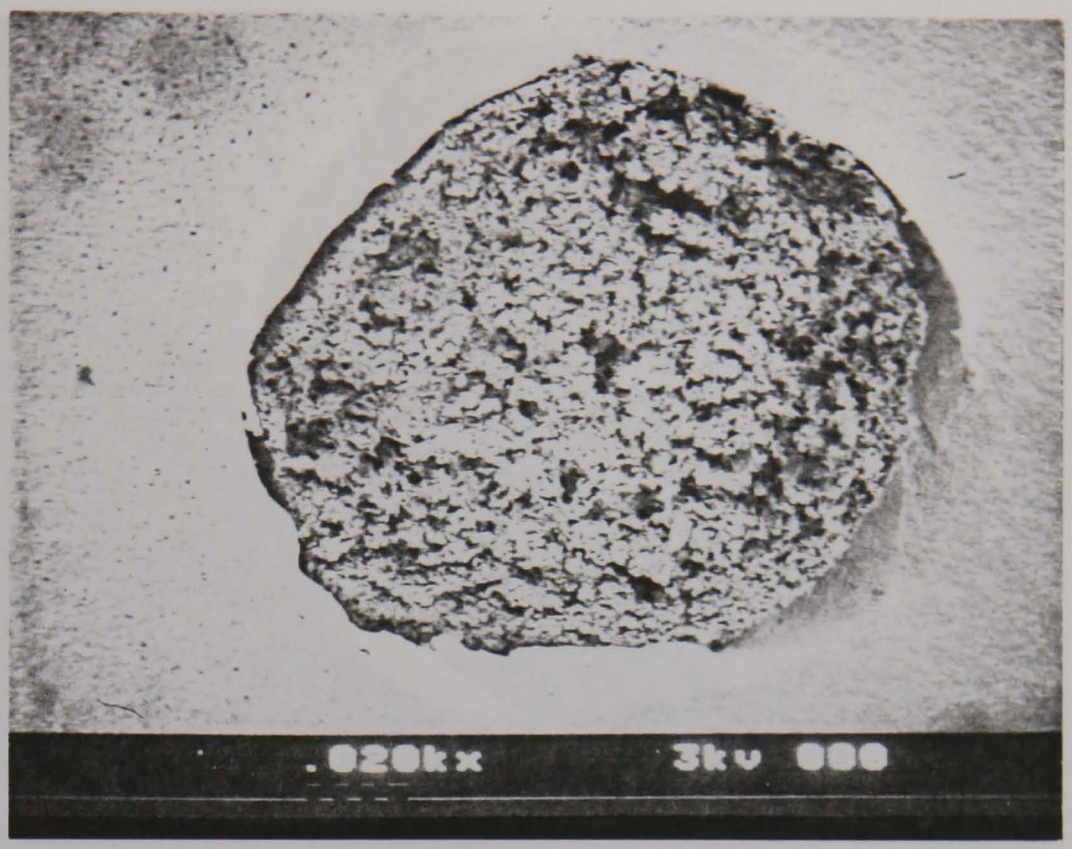


Figure 4.40a. SEM of pellet cross-section coated with Silicone Elastomer 4:1 (post-dissolution); x80.

Figure 4.40b. SEM of pellet cross-section coated with Silicone Elastomer 4:1 (post-dissolution); x400.

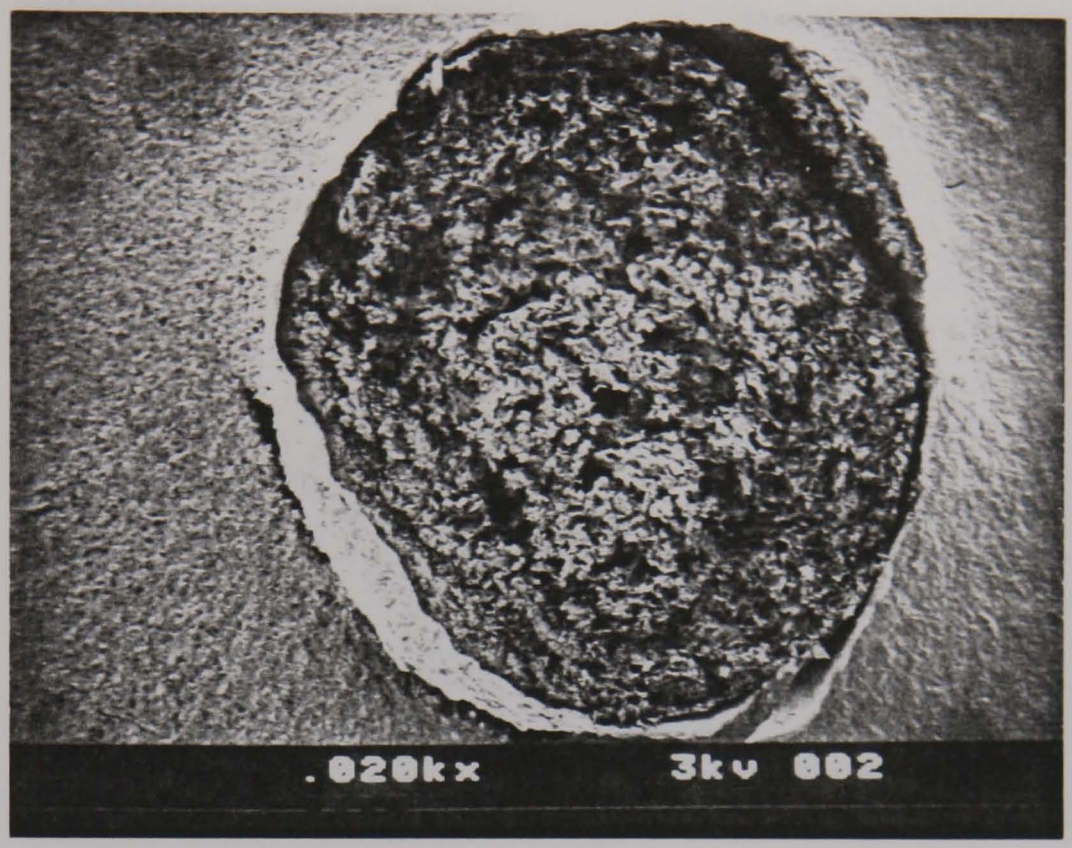


Figure 4.41a. SEM of pellet cross-section coated with Silicone Elastomer 6:1 (post-dissolution); x80.

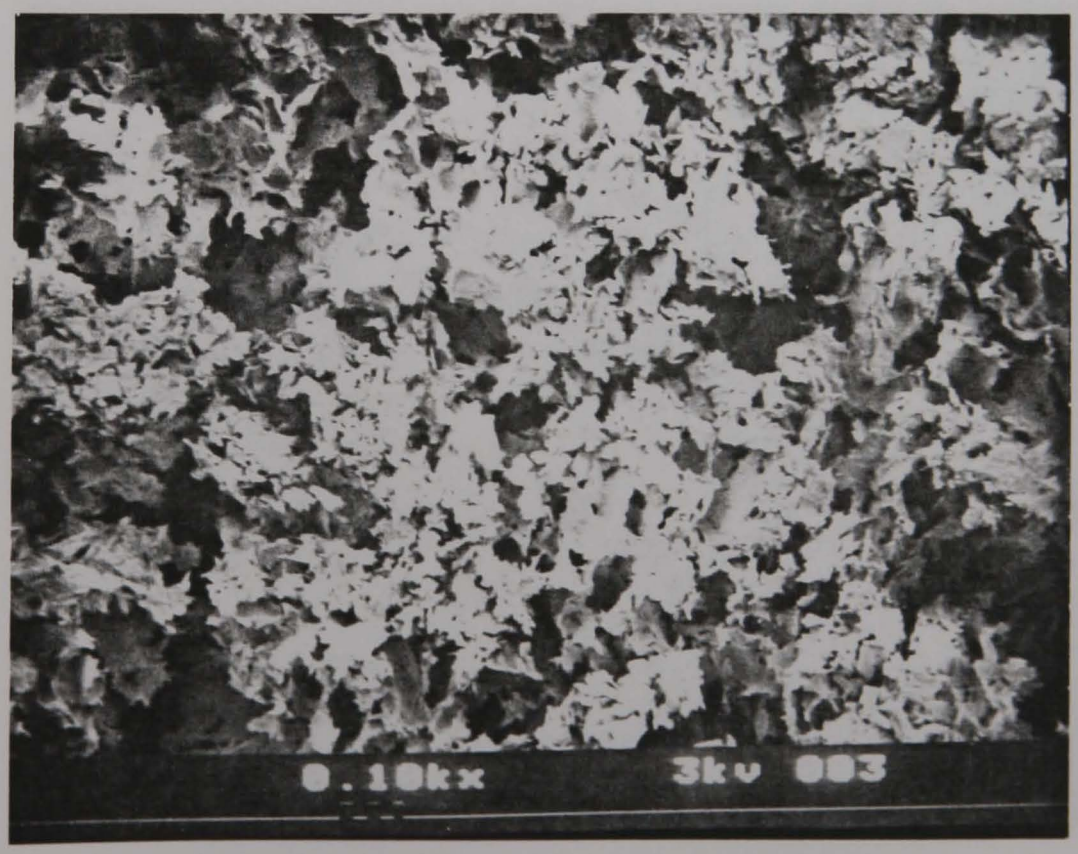


Figure 4.41b. SEM of pellet cross-section coated with Silicone Elastomer 6:1 (post-dissolution); x400.

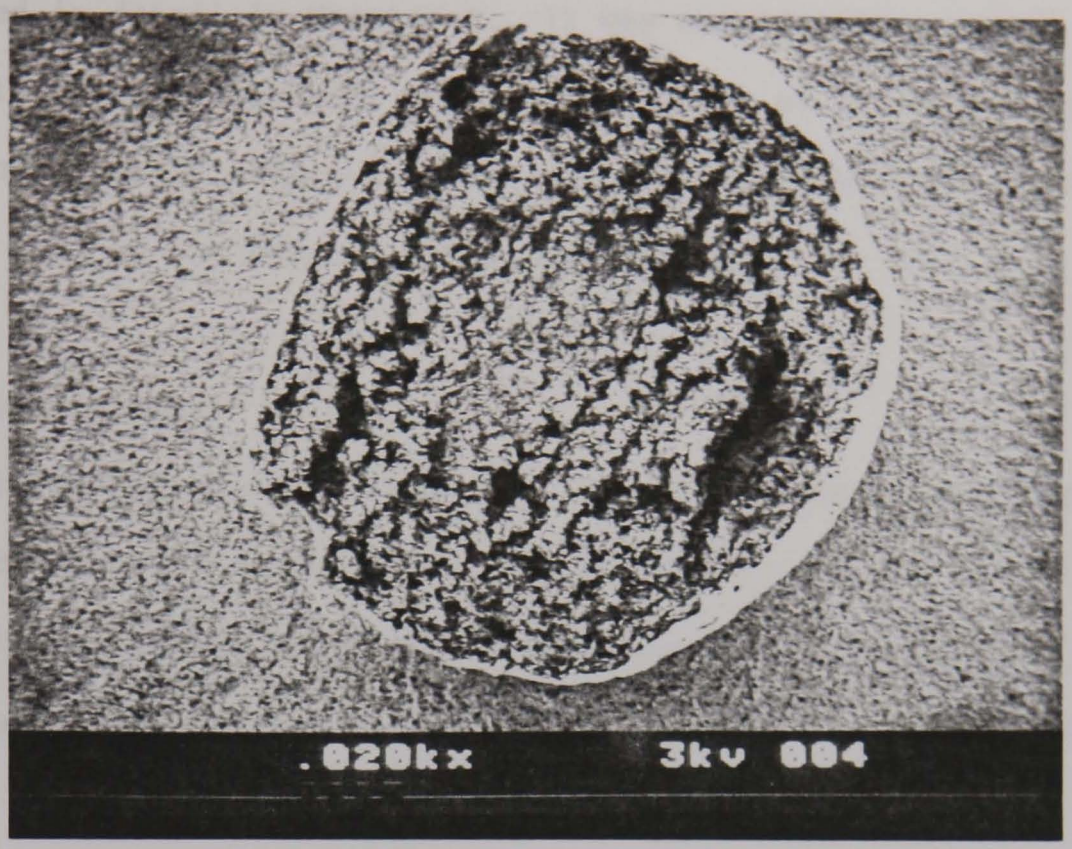


Figure 4.42a. SEM of pellet cross-section coated with Silicone Elastomer 2:1 + 10% PEG (post-dissolution); x80.

Figure 4.42b. SEM of pellet cross-section coated with Silicone Elastomer 2:1 + 10% PEG (post-dissolution); x400.

The mechanical properties of free-films of Silicone Elastomer are discussed in detail in Chapter 5. It was considered necessary to be able to quantify the fundamental tensile properties of the free-films in order to demonstrate the relative abilities of the polymer systems to withstand applied load in the form of pellet compaction.

4.4. Conclusions.

The incorporation of ibuprofen into an uncoated pellet formulation with microcrystalline cellulose (Avicel PH101), results in the formation of multiparticulates which are essentially spherical porous matrices. Drug removal by *in-vitro* dissolution from pellet cores containing as much as 80%w/w drug and therefore only 20%w/w microcrystalline cellulose, yields visibly intact spheres.

Using the technique of scanning electron microscopy under high magnification to examine pellet surface and cross-sectional characteristics, it is apparent that drug has been leached from the pellet cores resulting in a fine tortuous skeletal network of microcrystalline cellulose.

Drug release from uncoated pellets containing ibuprofen appears to exhibit first-order kinetics and is remarkably sustained even when the initial drug loading is as high as 80%w/w.

The application of a polymeric membrane in the form of an aqueous dispersion to spherical multiparticulates, has the effect of retarding the rate of drug release. There appears to be a critical coating level, below which core coverage by the polymer is incomplete and drug release is diffusion controlled and first-order kinetics are observed. Above this critical coating level, drug release appears to become membrane controlled and zero order kinetics are observed; the drug release rate becomes time independent after a minimum polymer level has been achieved.

The presence of plasticiser within the coating formulation, not only

influences the glass transition temperature of the polymer and the elasticity of the film, but it imparts a hydrophilic component to an otherwise extremely hydrophobic membrane. As a consequence of the *in-vitro* dissolution of plasticised polymer coated pellets, penetration of aqueous solvent molecules into and drug release from the pellet core, is enhanced by the creation of hydrophilic pores which are formed in the polymeric membrane by the leaching of the plasticiser into the dissolution medium.

Polymeric membranes derived from aqueous dispersions and applied to pellets using the methodology described in detail in Chapter 3, enables polymer coalescence and complete film formation under the operating conditions of the coating chamber. This is characterised by the *in-vitro* drug release profiles for coated pellets containing ibuprofen, which were subjected to an additional "curing" stage involving 24 hours storage at 40°C following coating. There is negligible difference between the release of ibuprofen from those pellets exposed to this additional "curing" stage and those which were not. It may be concluded therefore that complete film formation and polymer coalescence was facilitated by the equilibrium conditions within the coating chamber for the three polymer systems studied.

The incorporation of plasticiser into the Silicone Elastomer aqueous emulsion leads to an enhanced rate of drug release and also appears to enhance the cohesion between the uncoated pellet surface and the polymeric membrane. Increasing the ratio of silicone to silica in the emulsion formulation, leads to a decrease in the rate of drug release and this appears to be reflected in the quality of the film coat. The presence of polyethylene glycol in emulsion formulations containing silicone to silica ratios in excess of 2:1, results in sticking and product agglomeration during the coating process.

It is evident on drug removal from pellet cores, that for this drug

and using the massing, extrusion and spheronisation techniques described in Chapter 2, that drug is evenly distributed throughout the cores, which even following drug removal are able to retain their physical shape and integrity. The interparticulate voidage exhibited by drug depleted pellets initially loaded with a high percentage of drug, is greater than that voidage created by the removal of drug from pellets initially containing a lower drug content.

CHAPTER 5

STUDY OF THE TENSILE PROPERTIES OF SOME FREE POLYMERIC FILMS PREPARED FROM AQUEOUS DISPERSIONS

5.1. Introduction.

It is proposed that a consideration of the tensile properties of the aqueous polymeric dispersions used to form the release-retarding membranes applied to the ibuprofen pellets in this study, will give an indication of the ability of the coating to withstand the compression process in the formation of the tablet.

A study of the indentation hardness and tensile properties of free films is made in this work. By quantifying the physical properties of the film coating it is possible to gain insight into any damage that may occur during compression. *In-vitro* release studies (Chapter 7) have indicated that some damage is occurring to the polymeric membrane as a result of pellet compression; it was the aim of this work to establish and quantify where possible, the effect of compression as the causative factor of film splitting, cracking or peeling from the substrate.

In any pharmaceutical film coating operation in which a polymer film is applied to a substrate surface, cohesive forces exist between the film forming polymer molecules and adhesive forces exist between the film and the substrate. The term cohesion has been defined by Banker (1966) as the ability of the contiguous surfaces of the same material at a molecular level, to form a strong bond which prevents or resists separation at the point of contact. Complete film formation from an aqueous dispersion of a water-insoluble polymer requires the coalescence of the polymer particles and consequential disappearance of the boundary layers between adjacent polymer molecular layers or surfaces. This is facilitated by the diffusion of individual macromolecules or segments of macromolecules between and within film layers.

5.1.1. Film preparation.

Kanig and Goodman (1962) described methods of preparing and studying free polymeric films and compared the properties of free films prepared

by casting and by conventional spraying techniques. A major differentiating factor between sprayed and cast films is that the mechanism of sprayed film formation involves the build up of contiguous layers of polymer on the substrate. It is proposed that at least some of the particles of the spray-dried polymer and air may become entrapped leading to imperfections in the structure of the film. Free-film preparation by the pouring of an aqueous polymeric dispersion can lead to an enhanced susceptibility of the dispersed particles to segregate. This is a consequence of the lengthy drying times necessary with such systems and may result in films consisting of multiple dissimilar layers. This separation does not occur in the film coating of tablets by conventional spray techniques (Allen et al. 1972).

Aulton (1982) argued that free-films prepared by spraying provide a more realistic model of the coating on a tablet substrate whilst films prepared by pouring are easier to prepare to the desired thickness with freedom from bubbles and defects. This author states that casting is a more accurate method for achieving data on the fundamental properties of the polymer and the polymer formulation. Kanig and Goodman (1962) discussed the benefits of studying the properties of free-films without introducing the variables associated with the casting technique.

Zaro and Smith (1972) described a technique to enable study of the effect of casting and spraying films onto similar tablet substrates. This consisted of a Teflon-coated plate with holes to accommodate the tablets, such that a single tablet surface was exposed to the coating formulation.

It may be concluded from the literature that poured or cast films offer a means of studying the fundamental properties of polymers, whilst sprayed films more accurately simulate a polymeric membrane applied to the surface of a tablet substrate by commercial spraying techniques.

Lindholm et al. (1987) studied the properties of free ethyl

cellulose films containing surfactant and particulate matter. Free films were prepared by casting and spraying an organic solution of ethyl cellulose. The results based on release curves and micrographs indicated that differences in structure and permeability between cast and sprayed films were small. These authors showed that for sprayed films, the effect of film thickness on elongation was minimal but that breaking strength increased with increasing film thickness. Lindholm et al. also showed that with this system thin poured films were mechanically stronger than sprayed films.

Devereux (1988) studied techniques for preparing free films from aqueous polymeric dispersions by pouring them onto various substrate surfaces. Parameters studied included the tendency of the film to adhere to the substrate surface and the ability of the dispersion to spread uniformly on the substrate surface. Substrates studied were glass, silicone coated glass, PTFE coated glass, perspex, foil and PTFE sheeting. PTFE sheeting was most favourable for this laboratory test in that adherence of the film to the substrate surface was minimal, although dispersion spreading was considered to be poor. Consequently Devereux described a technique for the casting of free-films from aqueous polymeric dispersions onto the inner surface of a rotating PTFE cylinder. This technique and the apparatus used in this study are described subsequently in section 5.2.

5.1.2. Viscoelastic materials.

The effect of stress σ on an ideal viscous liquid and on an ideal elastic solid may be predicted from Newton's Law (Equation 5.1) and from Hooke's Law (Equation 5.2) respectively. Newton's Law states that shear stress σ (Pa) is proportional to the rate of strain ($d\epsilon/dt$), where n is the viscosity (Pa s):

$$\sigma = n\ (d\epsilon/dt) \qquad \text{Equation 5.1.}$$

Hooke's Law states that shear stress σ is directly proportional to strain ϵ

$$\sigma = G\,\epsilon \qquad \text{Equation 5.2.}$$

where G is the modulus of elasticity (Pa). A spring with a modulus of G and a dashpot containing liquid with a viscosity n, have been used as models for Hookean elastic solids and Newtonian liquids respectively. In these models the spring stores energy in a reversible process and the dashpot dissipates energy as heat in an irreversible process. Figure 5.1 is a stress-strain curve for a typical elastomer; the straight dashed line indicates Hookean behaviour as described in Equation 5.2. It is evident that the elastomer behaviour is not Hookean.

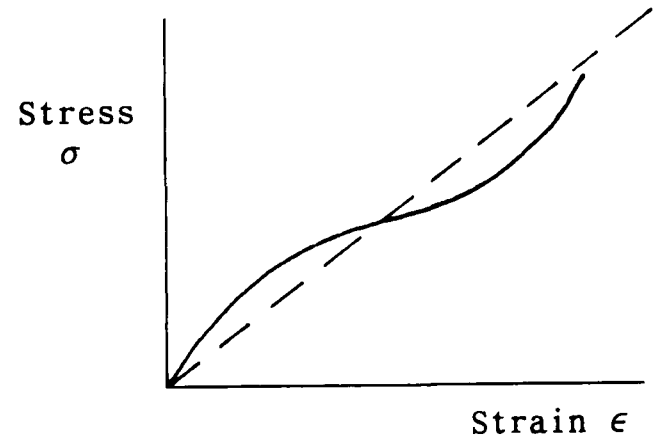


Figure 5.1. Stress-strain curve for a typical elastomer. The dashed line indicates Hookean behaviour.

Elastomers and synthetic polymers exhibiting both viscous flow and elasticity are termed viscoelastic. The work done in deforming a Hookean solid is recovered completely when the body is restored to its original shape. However the work done in deforming a body exhibiting Newtonian flow is used to maintain flow and is converted completely into heat by the friction between the molecules or particles in the liquid. It is this internal friction which is responsible for viscosity. When a viscoelastic material is stressed some of the work done is stored

elastically and can be recovered and the rest is dissipated as heat in maintaining flow.

For most plastic materials, as an approximation, elasticity predominates at low stresses and viscous flow at high stresses; the two types of behaviour being separated by the yield stress. With all viscoelastic materials, elasticity and flow occur simultaneously. Rheological models describing the behaviour of viscoelastic materials contain springs and dashpots and which may be connected in series (Figure 5.2) or in parallel (Figure 5.3).

A viscoelastic liquid in which the slightest stress causes a permanent deformation in the form of viscous flow is represented by the Maxwell model (Figure 5.2).

Figure 5.2. Maxwell model for viscoelastic behaviour.

If the spring is considered to be strong, this model explains the elasticity of fluids such as liquids and gases. If the dashpot is considered to contain an extremely viscous oil, the model represents the slow creep of an elastic solid, including elastomers below their elastic limit (Wallwork and Grant, 1978).

A viscoelastic solid will eventually return to its original shape after a small deforming stress has been applied and removed. The simplest rheological model for this behaviour consists of a spring and dashpot in parallel and is known as a Voigt body (Figure 5.3).

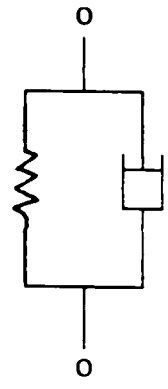


Figure 5.3. Voigt model for viscoelastic behaviour.

The elastic property predominates if applied stress is slowly increased or decreased and the body behaves like a solid. When the body is subjected to rapidly changing stress, the elastic deformation and recovery are retarded by the viscous property of the material. Therefore if the body is subjected to an oscillating stress of high frequency and the viscous property predominates, the work of deformation is absorbed and the body behaves like a liquid. It is therefore apparent that the Voigt body and the Maxwell body show opposite time-dependent behaviour.

The magnitude of the elastic modulus (or "stiffness") of a polymer film is a function of intermolecular forces and additives within that film. For elastomers in which there is little cross-linking of polymer chains, the chains are able to move relative to each other and the material flows visibly under conditions of applied stress. Considerable cross-linking hampers movement of polymer chains thus preventing flow, reducing the elasticity and causing a hardening of the material. The amplitudes of the molecular motions and vibrations depends to a large extent on the temperature. For a given polymer the glass transition temperature (*Tg*) is the temperature above which the polymer is ductile due to the macromolecules possessing a certain freedom of motion. Below the *Tg* the polymer is relatively hard, brittle and glass-like as a consequence of the attractive forces between the macromolecules causing an apparent fixing of their positions.

The Maxwell model may be expressed mathematically as follows:

$$d\epsilon/dt + G/n = 0 \qquad \text{Equation 5.3.}$$

$$\sigma = \sigma_o \, e^{-t(G/n)} \qquad \text{Equation 5.4.}$$

where σ_o is equal to the initial stress before the stretched specimen is allowed to relax exponentially with time t. When $t = n/G$, the σ is reduced to $1/e$ ($1/e = 1/2.7 = 0.37$) times the original value. The relaxation time is equal to n/G. When a Maxwell model is subjected to an applied stress it first deforms instantaneously and then undergoes irreversible flow.

A viscoelastic solid will eventually return to its original shape after a small deforming stress has been applied and removed. The rheological model proposed by Voigt (Figure 5.3) in which the spring and dashpot are in parallel, the applied stress is shared and each element is deformed equally. Thus the total stress σ is equal to the sum of the viscous stress $n(d\epsilon/dt)$ plus the elastic stress $G\epsilon$:

$$\text{Total stress } \sigma = n(d\epsilon/dt) + G\epsilon \qquad \text{Equation 5.5.}$$

On integration Equation 5.5 becomes

$$\epsilon = \sigma/G \; (1 - e^{-tG/n}) \qquad \text{Equation 5.6.}$$

where the retardation time n/G is equal to the time for the stress to decrease to $(1 - 1/e)$ of the original value ($1 - 1/e = 1/2.7 = 0.63$).

Viscoelasticity is time-dependent since strain is not only a function of the magnitude of the stress at any given time, as is the case for an elastic solid (Hookean body), but is also a function of the rate of change of stress at any given time, as is the case for viscous or

Newtonian flow. Several Maxwell units arranged in parallel may be used to represent rheological behaviour, and several Voigt units arranged in series may be used to represent creep. It is not possible to accurately represent polymer behaviour with simple Maxwell or Voigt models, although they are able to mimic the type and relative importance of certain general types of behaviour on a molecular scale.

In a more practical way, Carswell and Nason have classified polymers on the basis of modulus into five categories, as shown in Figure 5.4: (a) soft and weak, (b) hard and brittle, (c) soft and tough (low modulus and high elongation), (d) hard and strong and (e) hard and tough.

It is important to note that the behaviour of polymers below the yield point is Hookean and essentially reversible in the short term. Thus the range, which is associated with the stretching and bending of covalent bonds, is called the elastic range. The area under the stress-strain curve is a measure of the toughness of the polymer.

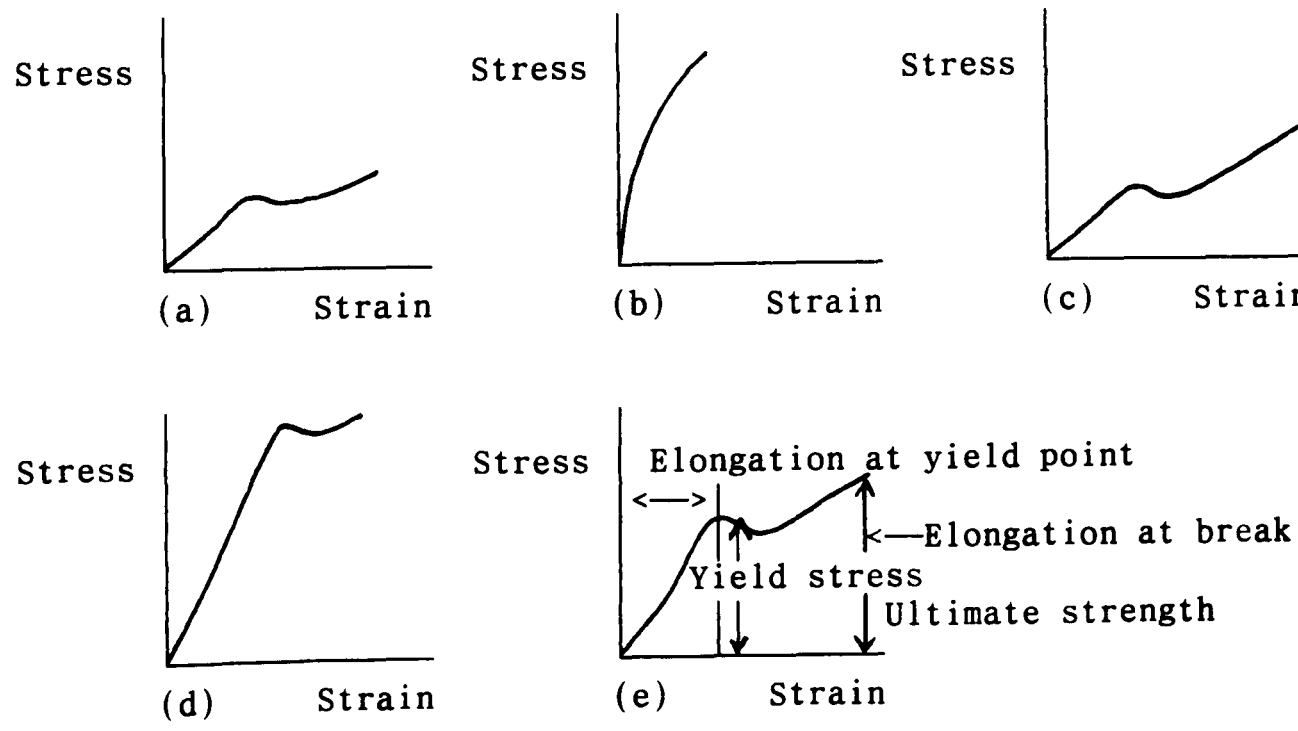


Figure 5.4. Typical stress-strain curves.

5.1.3. Indentation hardness.

Indentation testing involves measuring the penetration of an indenter tip under known load into a film coat, either *in-situ* or presented as a free-film mounted onto a fixed platen. The indenter tip will penetrate the film to a distance which is dependent upon the applied load and the rheological properties of the membrane itself. The indenter will travel a greater distance into a soft, elastic material as compared with a harder more brittle film. Indentation testing yields information relating to the resistance to deformation and the elasticity of the polymeric material.

This work involved a study of the effect of the nature of the polymer and the presence of other excipients forming the film, on the elastic modulus, the Newtonian viscosity, instantaneous and time-dependent elastic creep compliance.

Aulton (1982) discusses definitions of hardness and indicates probably the most accurate to be that of Braun (1958); "hardness is the quasistatic resistance to local non-homologous deformation caused by point or line shaped force centres". The British Glossary of Paint Terms described hardness of paint film coatings as the ability of the coating, as distinct from its substrate, to resist indentation of penetration by a hard object. Aulton discusses the relevance of this to pharmaceutical systems in which films are applied to pharmaceutical dosage forms, with particular reference to tablets, and the fact that the indentation load must be carefully selected such that the depth of indentation by any given load does not exceed 1/6 of the thickness of the film under test.

Hardness is quantified in terms of the load applied to indenter divided by the area beneath the indenter tip supporting that load. It therefore has units of pressure (Pa or Nm^{-2}). For a spherical indenter tip, hardness data such as Brinell and Meyer's have been used in respect of pharmaceuticals.

Brinell Hardness is defined as the ratio of applied load to the curved area of indentation:

$$\text{Brinell Hardness} = \frac{\text{load}}{\text{curved area of indentation}} \qquad \text{Equation 5.7.}$$

$$= \frac{2F}{\pi D\,[D - \sqrt{(D^2-d^2)}]} \qquad \text{Equation 5.8.}$$

$$= \frac{F}{\pi D h} \qquad \text{Equation 5.9.}$$

where F is the applied load, D is the diameter of the indenter tip, h is the depth of penetration and d is the diameter of the indentation in the plane of the surface (Figure 5.5).

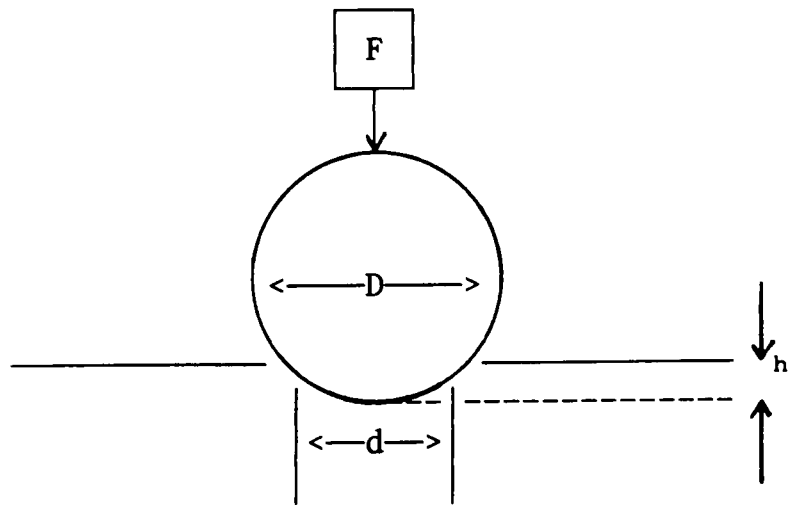


Figure 5.5. Geometry of sphere indentation.

Meyer's Hardness is defined as a ratio of the applied load to the projected area of indentation:

$$\text{Meyer's Hardness} = \frac{\text{load}}{\text{projected area of indentation}} \qquad \text{Equation 5.10.}$$

$$= \frac{F}{\pi d^2} \qquad \text{Equation 5.11.}$$

An advantage of Meyer's definition is that it more closely approximates the mean pressure beneath the indenter.

However due to the time-dependent deformation of films under applied load, even quoting hardness values calculated by measuring film penetration by the indenting load at a given time, does not necessarily guarantee that all polymers will have similar deformation characteristics as a result of a given penetration time (Aulton, 1982).

Aulton (1982) discusses possible solutions to this problem. A mathematical alternative involves the derivation of some time-dependent viscoelastic parameters by the generation of creep compliance curves.

5.1.4. Creep compliance.

Creep is the name of the phenomenon in which strain deformation increases with time, when a constant stress is applied to a viscoelastic material. When the stress is removed, the deformation will usually decrease, a process which is termed recovery. During recovery the strain falls to an equilibrium value which is usually higher than the initial value before deformation, as a consequence of viscous flow. Aulton (1982) describes the following equation originally presented by Lee and Radok (1960):

$$J_c(t) = \frac{16\sqrt{R}}{3F} [h(t)^{3/2}] \qquad \text{Equation 5.12.}$$

where $J_c(t)$ is strain/stress or creep compliance at time t $(MPa)^{-1}$, R is the radius of the indenting sphere, F is the indentation load and h(t) is the depth of indentation at time t. Equation 5.11 enables calculation of creep compliance at time t and the results may be plotted as shown in

Figure 5.6. This presentation of viscoelastic behaviour enables polymer definition in terms of the Maxwell and Voigt spring and dashpot models described previously. The instantaneous elasticity (AB) and the instantaneous recovery (CD), are attributed to the spring in the Maxwell model (Figure 5.6). The delayed or retarded elasticity (BC) and the delayed or retarded recovery (DE) are due to the Voigt model. The dashpot in the Maxwell model explains the viscous deformation J_N remaining after recovery.

The ratio of the strain (due to creep) at a given time to the constant stress is termed the creep compliance ($N^{-1}m^2$ or Pa^{-1}) at that time.

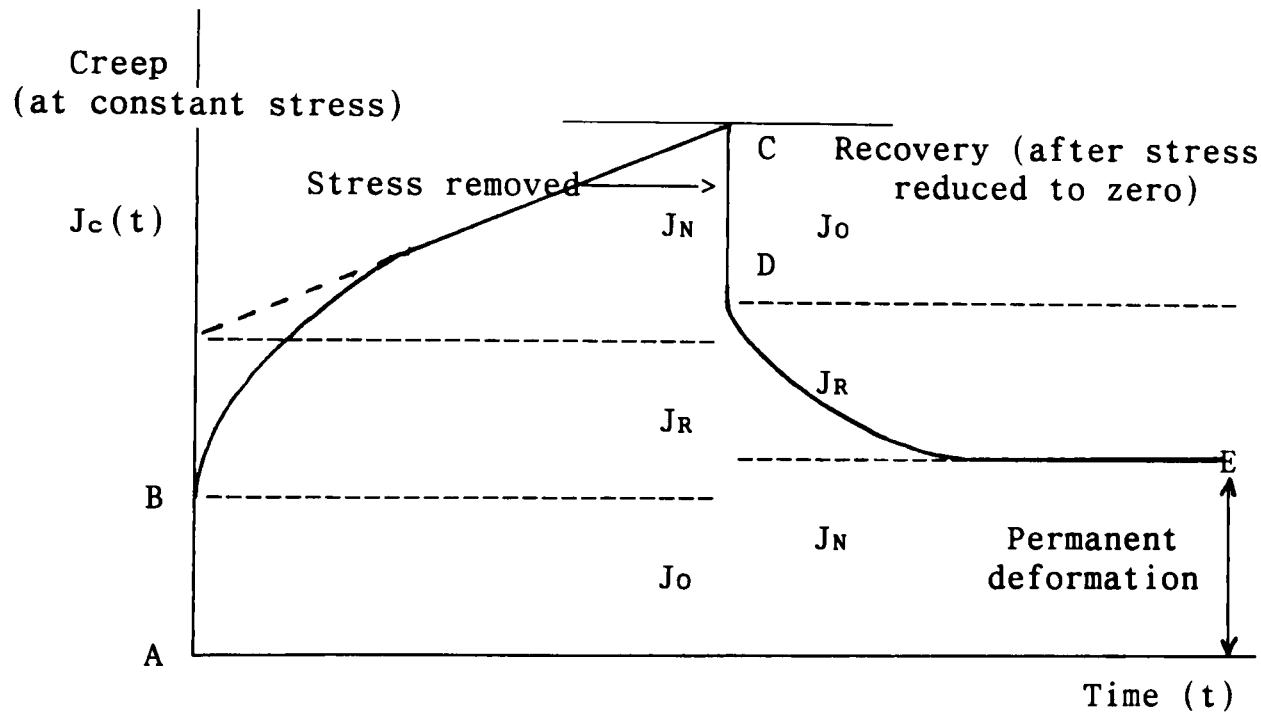


Figure 5.6. Idealised creep compliance versus time profile for a viscoelastic material.

Figure 5.7 illustrates how the Maxwell and Voigt models may be combined to define a polymer coat (Aulton, 1982). J_0 to J_3 are the compliance of the elastic elements and n_1 to n_N are the effective viscosities of the dashpots.

Indentation rheology of polymeric materials reveals that the elastic component of such materials is attributable to multiple components. The

instantaneous elastic or Hookean component is associated with the bending or stretching of valency bonds. Films displaying these characteristics alone will be brittle and exhibit a small elongation at break.

Secondly, a retarded elastic component which is time-dependent and is represented by the Voigt model occurs as a result of uncoiling disentanglement and partial alignment of the molecular chains: in this situation the modulus is much lower. It is also possible that the chains of the polymer molecules may also slip over each other, resulting in viscous deformation only; this may be represented by the dashpot model alone. The total deformation which is the sum of the above three types of deformation exhibit time-dependent properties.

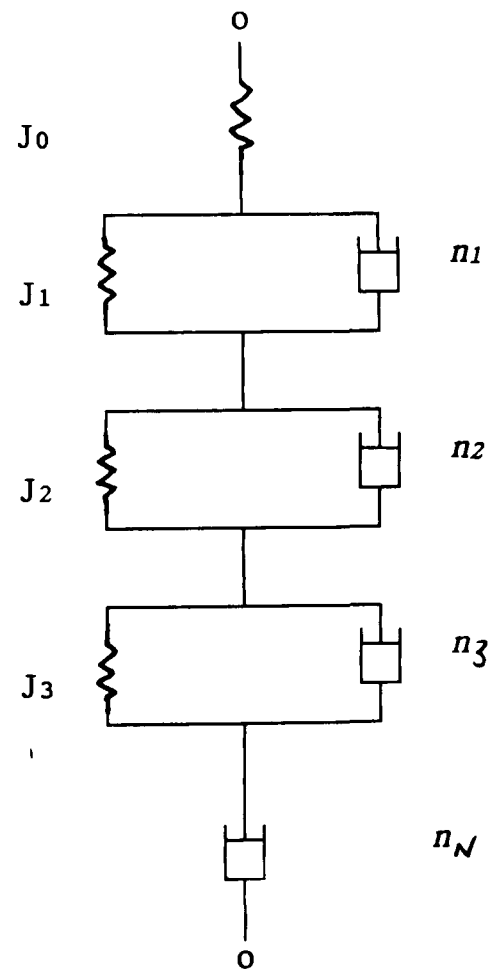


Figure 5.7. Diagram showing combination of Maxwell and Voigt models illustrating viscoelastic properties of polymer films.

5.2. Methods.

5.2.1. Aqueous polymeric dispersion preparation.

It was the aim of this part of the study to quantify the mechanical properties and thus determine the ability of polymeric films prepared from aqueous dispersions to retain their integrity as a consequence of pellet compression.

Aqueous polymeric dispersions were prepared using the methodology described in section 3.2.

5.2.2. Free-film preparation.

A film casting substrate must facilitate uniform spreading of the film causing minimal adherence of the film to its surface. The resultant film must be of uniform thickness, of smooth surface and free from air bubbles. The film must be free from any particulate contamination and was therefore cast onto a grease free surface, by prior treatment with industrial methylated spirit. Film casting by pouring resulted in the tendency of the aqueous dispersions to form "islands" when in contact with the hydrophobic surface of grease-free Teflon or glass surfaces. Also the relatively low viscosities of these aqueous dispersions as a consequence of being composed of solid polymer dispersed in an aqueous phase, rendered the formation of uniform films prepared by pouring onto a substrate surface, both glass and Teflon, impossible. This is in stark contrast to film casting by pouring for organic or indeed aqueous solutions of many water-soluble polymers, which are inherently of greater viscosity and therefore not susceptible to incomplete spreading and "island" formation when in contact with a hydrophobic grease-free Teflon or glass substrate.

Any film adhering with a high affinity to a substrate surface, even if it were possible to be separated from that surface, is susceptible to damage as a consequence of being detached from the casting surface. Any

induced strain or stress or elongation as a consequence of this process, inherently has an adverse effect on the properties of that polymeric membrane. In the course of this work, aqueous dispersions were poured onto Teflon, glass and perspex Petri dishes, both directly and by means of a TLC applicator, and dried at room temperature (RT), typically 18-20°C, under ambient conditions and in also a hot air oven for 24 hours at 30, 45 and 60°C. No satisfactory films were prepared by this method; films were either of uneven surface characteristics due to the presence of air bubbles, were non-detachable from the substrate surface, or of too great a thickness to be of value for quantitative evaluation. Details of unsuccessful techniques are summarised subsequently (Table 5.1).

Initial studies for evaluating a suitable technique for the preparation of free films composed of aqueous polymeric dispersions were made using a dispersion containing Eudragit RS30D 35.5%w/w, Eudragit RL30D 9.05w/w, plasticised with triethylcitrate (Citroflex 2) 2.67%w/w and containing Syloid 244FP 4.0%w/w. Syloid 244FP is a colloidal grade of silicon dioxide and was used in aqueous coating dispersions containing polymethacrylate to prevent pellet agglomeration and adherence under the operating temperatures of the film coating chamber.

The virtues of free-film preparation by pouring and spraying techniques have been discussed in section 5.1. The importance of the operating conditions necessary for complete film formation and polymer coalescence of films prepared from aqueous dispersions have been documented previously in Chapter 3.

In an attempt to reproduce those conditions created within the coating chamber during the coating of pellets, it was attempted to prepare free films by spraying an atomised dispersion in a warm-air environment (40-45°C) by means of a fan heater, created within a fume cupboard. It was not possible to control the air temperature adequately or to create conditions conducive for film formation and polymer

Substrate surface	Method of application	Drying conditions
glass	TLC applicator	RT 30°C 45°C 60°C
	spraying	40-45°C
Teflon	TLC applicator	RT 30°C 45°C 60°C
	spraying	40-45°C
	pouring	RT 30°C 45°C 60°C
Perspex (Petri.dish)	pouring	RT 40°C

Table 5.1. Summary of unsuccessful film casting techniques.

coalescence using this procedure. All that was achieved was a dried film of previously dispersed particles with a high affinity to both glass and Teflon.

The technique of Devereux (1988) was adapted to facilitate the formation of uniform smooth surface films, free from air bubbles. These were prepared from aqueous polymeric dispersions by casting onto the inner surface of a hollow lipped rotating cylinder made of polytetrafluoroethylene (PTFE). The cylinder had detachable lips lined with polythene, of internal diameter slightly smaller than that of the main body of the cylinder (see Figure 5.8). The cylinder was placed on ball mill rollers rotating at 20 rpm. Hot air was directed onto the outer surface of the rotating cylinder from a fan heater through an opening in a perspex environmental box; the environmental box completely encased the cylinder (Figure 5.9). A contact thermometer was used to maintain

thermal equilibrium throughout the film-forming process and was positioned inside the cylinder along the horizontal axis and parallel to the walls of the film-forming surface. The contact thermometer was set to maintain a working temperature of 43°C. The temperature of the circulating air surrounding the rotating cylinder was monitored during film formation and throughout the 24 hour drying period (Table 5.2).

The apparatus was allowed to achieve thermal equilibrium by running for a two hour period prior to film casting. The required quantity (typically 60g) of aqueous film coating dispersion was then poured into the rotating PTFE cylinder by means of a glass funnel attached to a length of silicone tubing. Immediately after pouring the dispersion into the cylinder, the lid of the surrounding box was closed in order to minimise the tendency for temperature fluctuation and a deleterious effect on the thermal equilibrium established during the warm-up period.

Cylinder rotation speed	20 rpm
Contact thermometer setting	43°C
Fan Heater Setting	1 kW
Environmental box temperature a) T_1 (opposite heat source) b) T_2 (extreme end of box)	 45 - 55°C 38 - 42°C
Pre-warming time	2 hours
Drying time	24 hours
Weight of dispersion	60 g

Table 5.2. Operating Variables of the Film Casting Technique using a Rotating PTFE Cylinder.

During evaporation of the aqueous phase of the polymeric dispersion (which took approximately 2 hours), the heat energy supplied by the circulating warm air is used to facilitate mass transfer; thermal equilibrium was maintained by the contact thermometer.

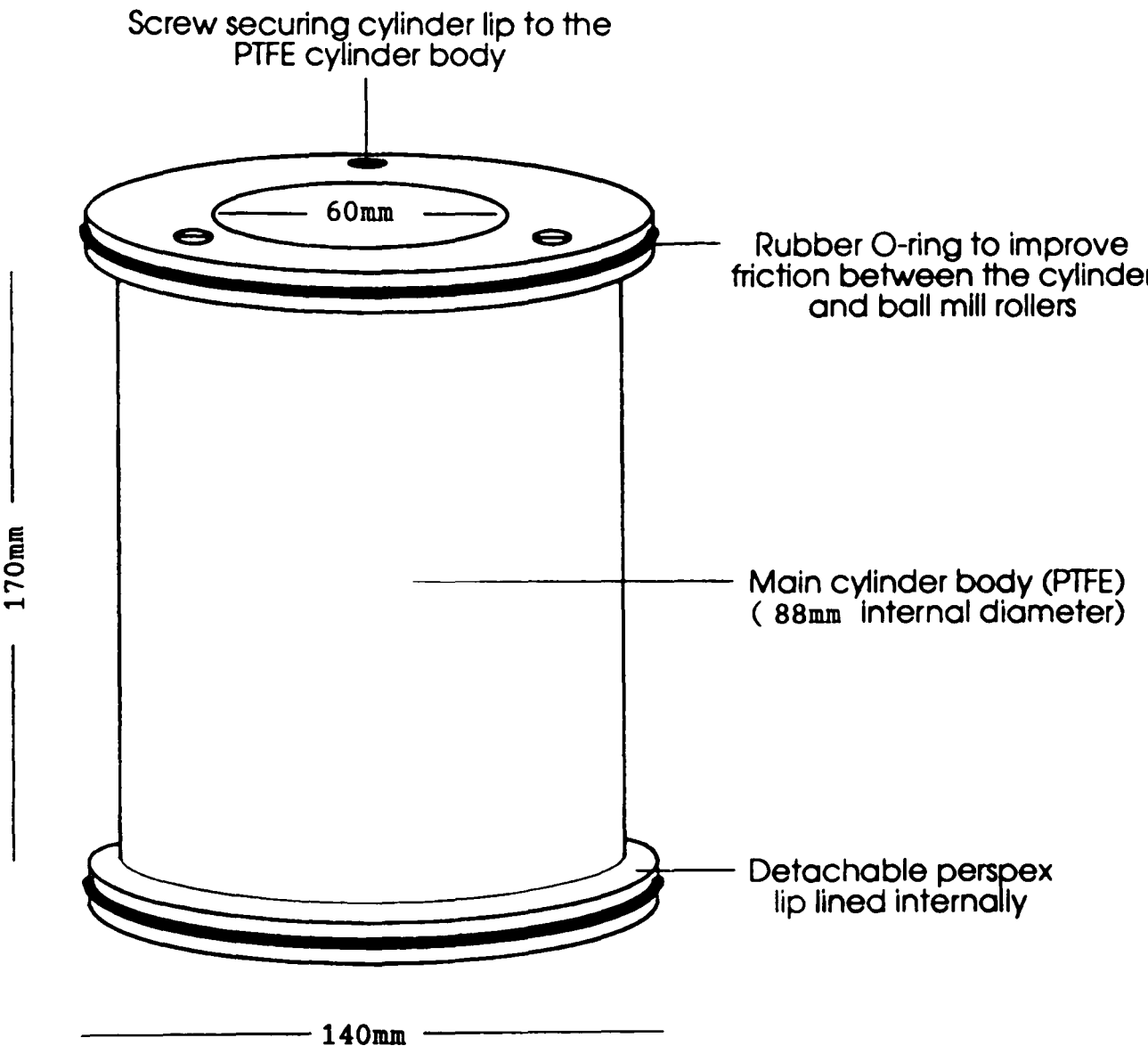


Figure 5.8. Diagram showing the PTFE rotating cylinder construction used in the film casting of aqueous polymeric dispersions.

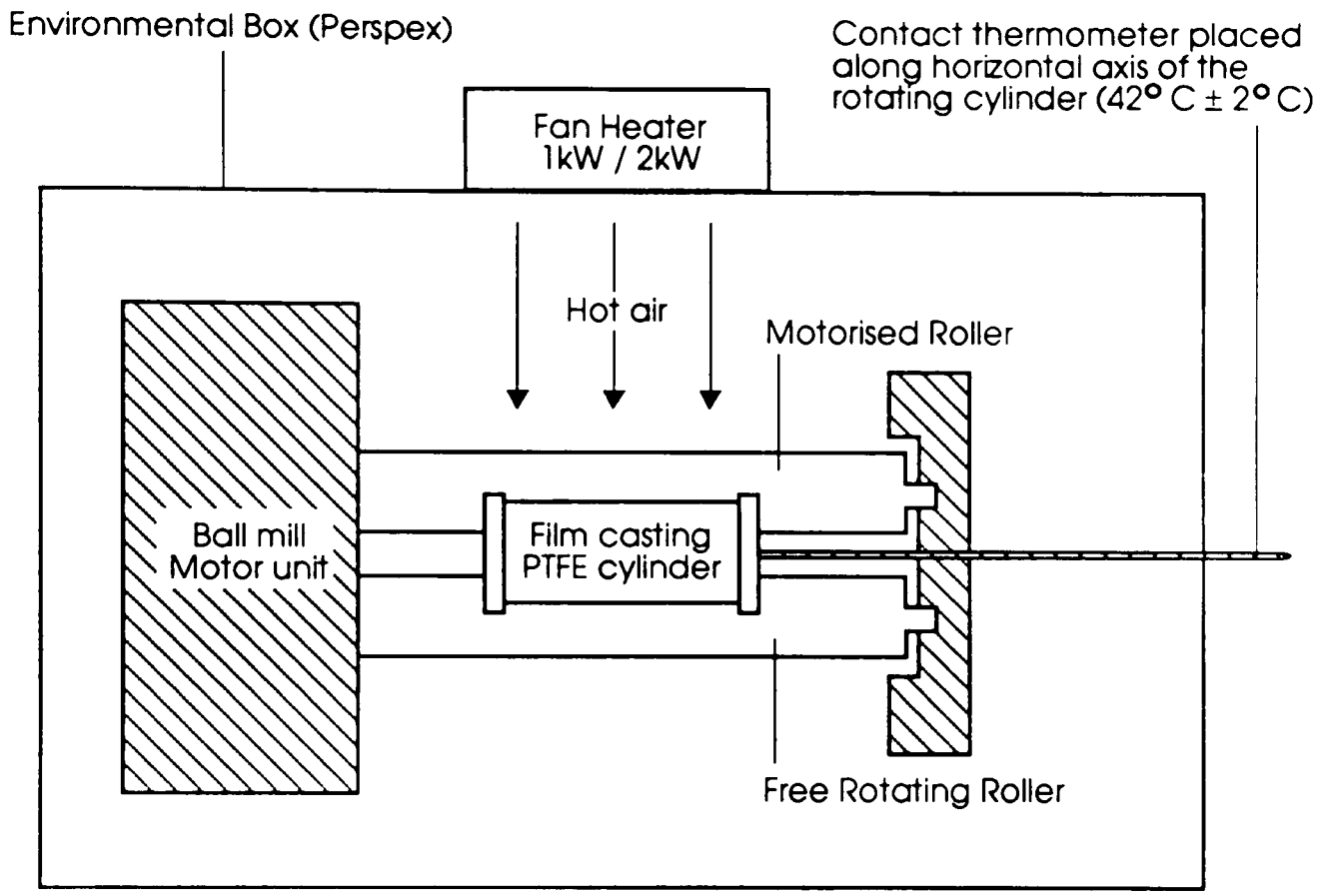


Figure 5.9. Schematic aerial diagram of the free-film casting apparatus.

Following evaporation of the aqueous phase, the temperature within the surrounding environmental box was seen to rise slightly. This is attributable to the fact that during water evaporation heat energy is absorbed as a consequence of mass transfer, whereas after water removal all energy is available for maintaining the temperature of the circulating air. Heat loss during the drying stage rather than the film forming stage occurs only as a result of conduction and convection: it is not required for mass transfer.

Films were carefully removed from the inner surface of the PTFE

cylinder, wrapped in aluminium foil and stored in airtight containers. The absorption of atmospheric moisture by the films was prevented by storing the foil wrapped films with a 250g silica gel sachet (Sorbsil Chemicals) in each airtight container. This was to enable assessment of the rheological properties of films without the influence of any sorbed moisture. Formulations of free polymeric films studied are detailed in Table 5.3:

Excipient	% w/w					
Eudragit RS30D	35.5	35.5	35.5	35.5	35.5	35.5
Eudragit RL30D	9.0	9.0	9.0	9.0	9.0	9.0
Citroflex 2	2.67	2.67	3.0	2.67	3.0	1.34
Syloid 244FP	4.0	2.0	4.0	-	-	-
Purified water BP to	100.0	100.0	100.0	100.0	100.0	100.0

a). Polymethacrylate Film Compositions

Excipient	%w/w
Surelease Dispersion (25% solids)	60.0
Purified water BP to	40.0

b). Ethylcellulose Film Composition

Ratio Silicone:Silica	2:1	4:1	6:1
Excipient		%w/w	
Silicone Emulsion X7-2837(A)	21.88	43.77	32.83
Colloidal Silica X7-2837(B)	34.10	34.12	17.06
Purified water BP to	100.00	100.0	100.0

c). Silicone Elastomer Film Compositions

Table 5.3. Aqueous Polymeric Film Formulations Prepared by Film Casting.

5.2.3. Indentation hardness of free-films.

5.2.3.1. Apparatus.

The apparatus employed in the determination of the rheological properties of films prepared from aqueous polymeric dispersions was the ICI Micro-Indenter (Figure 5.10). The apparatus consists of a steel triangular main chassis, supported on a base plate by means of three adjustable legs. Coarse and fine adjustments of the raising or lowering of the platform or for zeroing of the instrument are facilitated by means of two of the three mounting legs. The coarse adjustment has a single screw thread of 20 threads per inch (20tpi). The fine adjustment has a differential thread of 26tpi and 28tpi, such that one revolution of the adjustment wheel gives a vertical movement of 20 micrometers at the position where the test sample is mounted. This wheel is graduated in divisions of 0.5 micrometers and is used to calibrate the instrument.

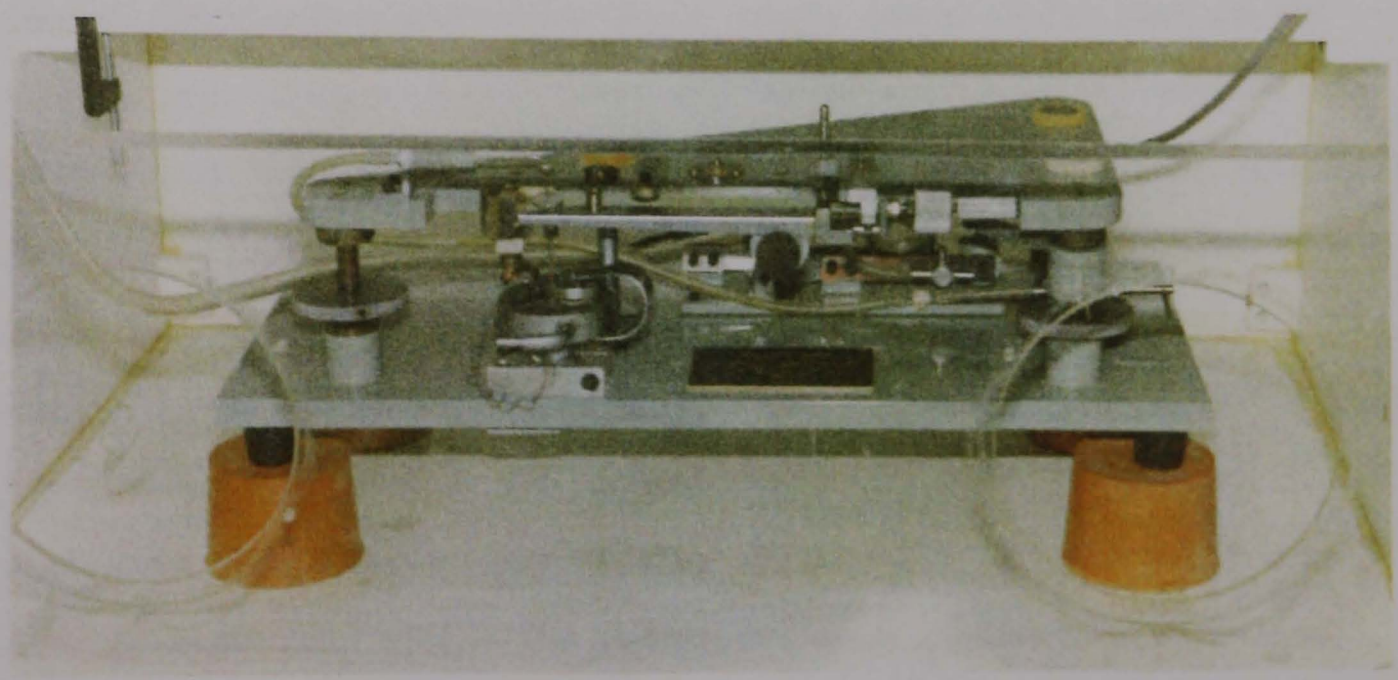


Figure 5.10. Photograph showing the ICI Micro-Indenter.

A beam mounted on brass crossed flexure bearings has adjustable counterbalance weight at one end. At the other end of the beam is an adjustable weight for setting the neutral stability or balancing the beam, an oil-filled dashpot damper and an indenter needle, a saphire sphere of 1.550mm diameter.

The original apparatus was modified such that a steel armature sub-miniature linear variable differential transformer (LVDT) core, (model 222-00005, RDP Electronics, Wolverhampton) was fitted, in place of the original pneumatic amplifier (Houghton, 1990). The depth of penetration of the steel armature into the body of the LVDT was energised by the output of the LVDT, and was accurate to $\pm$ 0.1μm.

The test specimen was mounted on a rigid platform situated just below the indenting sphere of the indenter needle. The indenting load was pneumatically lowered onto the beam by means of a bellows system, immediately above the indenter needle. As the sample was indented, the vertical movement of the indenter sphere and therefore the depth of indentation was gauged by a change in output from the LVDT. An amplifier (model 2027A) and a stabilised power supply (model 2031, both of RDP Electronics, Wolverhampton) energised the primary coil of the LVDT and demodulated the output of the secondary coils, giving a signal between 0V and 10 V d.c. at full scale displacement of the transducer. The amplifier gain was adjusted to give an output which was converted to a digital signal by means of an analogue-to-digital converter (ADC). This facilitated data logging and manipulation using a BBC Model B Microcomputer (Houghton, PhD Thesis, 1990).

In order to minimise the generation of erroneous results due to environmental conditions, the apparatus was mounted on rubber dampers designed to absorb vibration and within an environmental box in attempt to minimise excessive disturbance of the surrounding air during testing, in particular whilst the specimen was under applied load.

5.2.3.2. Sample preparation.

Samples of films of thickness approximately 100μm, cast using the rotating PTFE cylinder technique discussed previously (section 5.2.2) by means of a thin film of paper glue, were mounted onto glass cover-slips and allowed to dry under the storage conditions described previously for one hour prior to testing.

5.2.3.3. Indentation testing of prepared samples.

Each test sample was rigidly clamped directly below the tip of the indenter needle, a sapphire sphere of 1.550mm diameter facilitating sample indentation at low load thus enabling the determination of creep compliance of the test samples.

The indenting probe was gently lowered onto the surface of the sample until it just made contact with the film. The output of the LVDT at this point was zeroed electronically; this was recorded as zero penetration depth by the data logging system. The indenting load was lowered onto its stage above the indenter probe by means of a pneumatic bellows system. This facilitated uniform, reproducible and gentle load application to the sample. Data logging of time versus indentation depth commenced automatically on application of the load to the film causing a quantitatively determinable sample penetration. The voltage output of the LVDT during indentation was recorded as digital byte values; these values were then converted to displacement or depth of sample penetration values (μm). Logged data was stored on disc for subsequent retrieval, evaluation by discrete mechanical analysis and conversion into creep compliance curves by software specifically written for use with this apparatus (Houghton 1990).

The indentation load applied to each sample was designed to enable sample penetration of between 0 and 6μm over the duration of the test; the optimum penetration depth with respect to instrument calibration and

to ensure an indentation of less than 1/6 of the thickness of the film.

Indentation duration was sample specific and determined for each film formulation to ensure that a linear increase in creep compliance with time was established.

Table 5.4 shows the test variables for each film sample studied: these were determined experimentally and are sample specific. The indentation load required for a sample penetration of between 0 and 6 micrometers and also the indentation duration necessary for the establishment of linearity in respect of creep compliance is dependent upon the nature of the polymer forming the film, the quantity of plasticiser and the presence of other excipients.

Excipient	% w/w					
Eudragit RS30D	35.5	35.5	35.5	35.5	35.5	35.5
Eudragit RL30D	9.0	9.0	9.0	9.0	9.0	9.0
Citroflex 2	2.67	2.67	3.0	2.67	3.0	1.34
Syloid 244FP	4.0	2.0	4.0	-	-	-
Indentation load	3g	1g	3g	1g	1g	3g

a). Polymethacrylate Film

Surelease Dispersion	
Indentation load	1g

b). Ethylcellulose Film

Ratio Silicone:Silica	2:1	4:1	6:1
Indentation load	1g	0.5g	0.5g

c). Silicone Elastomer Films

Table 5.4. Effect of free-film composition on the indentation load necessary to cause a film penetration of less than 6μm.

5.3. Results and Discussion.

5.3.1. Creep Compliance of Free-Films.

Creep is the term given to a viscoelastic material in which strain deformation increases with time when a constant stress is applied. When the stress is removed the deformation will usually decrease, a process termed recovery. During recovery the strain falls to an equilibrium value which is usually higher than the initial value before deformation, as a consequence of viscous flow (Figure 5.6).

Briefly, the instantaneous elastic deformation (AB in the creep curve, Figure 5.6) and the instantaneous recovery (CD) are attributed to the spring in the Maxwell model. The delayed or retarded elasticity (BC) and the delayed or retarded recovery (DE) are due to the Voigt model. The dashpot in the Maxwell model explains the viscous deformation (E) remaining after recovery. In practice AB and BC may form a continuous curve, as may CD and DE, since elasticity and recovery are rarely instantaneous.

The compliance J_o, for the region of instantaneous elastic recovery (AB), is obtained by dividing the shear strain $\epsilon(t)$ measured at the onset of applied shear stress (at $t = 0$), by the shear stress σ.

$$J_0 = \epsilon(t)/\sigma = 1/G_0 \qquad \text{Equation 5.13.}$$

where G_0 is the shear elastic modulus.

The retarded elastic region, characterised by the region BC, has a compliance of J_R (Equation 5.14).

$$J_R = \epsilon_R(t)/\sigma \qquad \text{Equation 5.14.}$$

where $\epsilon_R(t)$ is the strain in this region.

The linear region of non-recoverable (Newtonian viscous) compliance J_N is given by

$$J_N = (t/n_0) = (\epsilon_N(t)/\sigma) \qquad \text{Equation 5.15.}$$

where n_0 is the apparent Newtonian viscosity of viscous flow and ϵ_N (t) is the strain. Bonds may actually rupture in this region and as a consequence the time required for them to reform is greater than the test period and the entities flow past each other.

On removal of the applied stress, there is some strain recovery. The region CD in Figure 5.6 represents the region of instantaneous elastic recovery and is the same magnitude as the initial elastic deformation (AB). This is followed by a retarded elastic recovery (DE) which is equivalent to (BC), the delayed or retarded elasticity. The viscous region J_N represents plastic deformation; this is permanent. Here bonds are irreversibly broken and the initial structure is not recoverable.

The results of hardness testing are influenced by many factors; examples include environmental vibration during application of the load, the condition of the specimen surface, the homogeneity of the film, the presence of any entrapped air, the thickness of the material and the location of the indentation. Indentation testing too close to previous indentation is liable to generate poor results, since the process of applying load to a polymer film can have the effect of causing work-hardening and/or a weakening of the area. Several readings were therefore taken for each sample such that the mean value was more representative of a given sample.

It is felt that the analysis of plastic deformation of polymer films by indentation testing provides a useful means of evaluating the mechanical properties of films and polymers themselves, particularly where films are directly subjected to applied stress, as in this work

during the compression of coated pellets.

Tables 5.5 to 5.14 inclusive, show the experimentally determined mechanical properties of the polymeric film formulations studied. Of particular interest are the instantaneous and the time-dependent elastic compliance data for these polymers and also the elastic modulus values. The instantaneous elastic compliance J_0 is obtained directly from the creep curve as time tends to zero. The elastic modulus G_0 is calculated as the reciprocal of J_0. The apparent Newtonian viscosity n_0 associated with the compliance of non-recoverable deformation is obtained from the slope of the late linear part of the creep compliance curve, since

$$J_N = t/n_0 \qquad \text{Equation 5.16.}$$

where the previous notation applies. The Newtonian viscosity therefore is inversely proportional at time t, to the non-recoverable viscous deformation $J_N(t)$. Hence a material exhibiting a large non-recoverable viscous deformation on the application of applied stress will have a correspondingly low apparent Newtonian viscosity; the converse is therefore also true.

The instantaneous elastic compliance (J_0) is as previously stated the reciprocal of the elastic modulus. Those materials displaying a relatively high instantaneous elastic component will therefore exhibit a relatively low elastic modulus.

5.3.2. Tabulated creep compliance data.

Free-Film Composition

Excipient	%w/w	% solids
Eudragit RS30D	35.50	10.65
Eudragit RL30D	9.00	2.70
Citroflex 2	2.67	2.67
Syloid 244FP	4.00	4.00
Purified water BP to	100.00	-
		20.02

Intercept on Y $J_R + J_o$ ($x10^{-8}$ Pa^{-1})	Instantaneous Elastic Compliance J_o ($x10^{-8}$ Pa^{-1})	Time-Dependent Elastic Compliance J_R ($x10^{-8}$ Pa^{-1})	Elastic Modulus G_o $x10^7$(Pa)	Newtonian Viscosity n_o $x10^9$(Pa s)
3.268	2.451	0.817	4.080	10.539
3.559	2.403	1.156	4.162	16.559
4.376	2.996	1.380	3.338	13.065
6.403	4.597	1.806	2.175	9.937
3.778	2.682	1.096	3.729	15.094
6.201	4.804	1.397	2.082	14.044
6.254	4.393	1.861	2.276	10.335
7.053	5.754	1.299	1.738	15.054
5.729	4.101	1.628	2.439	11.121
3.601	2.207	1.394	4.532	16.479
n 10	10	10	10	10
x 5.022	3.639	1.383	3.055	13.223
SD 1.439	1.240	0.321	1.024	2.583
%RSD 28.66	34.09	23.23	33.51	19.53

Table 5.5. Discrete Mechanical Analysis of a Polymethacrylate Film containing 2.67%w/w Plasticiser and 4.0%w/w Syloid.

Free-Film Composition

Excipient	%w/w	% solids
Eudragit RS30D	35.50	10.65
Eudragit RL30D	9.00	2.70
Citroflex 2	2.67	2.67
Syloid 244FP	2.00	2.00
Purified water BP to	100.00	-
		18.02

Intercept on Y $J_R + J_o$ ($x10^{-8}$ Pa^{-1})	Instantaneous Elastic Compliance J_o ($x10^{-8}$ Pa^{-1})	Time-dependent Elastic Compliance J_R ($x10^{-8}$ Pa^{-1})	Elastic Modulus Go $x10^7$(Pa)	Newtonian Viscosity n_o $x10^9$(Pa s)
20.166	11.612	8.554	0.861	1.568
11.070	7.285	3.785	1.373	3.153
10.820	6.420	4.400	1.558	2.657
13.566	8.222	5.344	1.216	3.171
13.784	9.279	4.505	1.078	2.190
15.084	8.067	7.017	1.240	3.755
15.497	9.253	6.244	1.081	1.415
19.411	11.343	8.068	0.882	2.204
13.927	7.596	6.331	1.316	2.111
n 9	9	9	9	9
x 14.814	8.786	6.028	1.178	2.469
SD 3.234	1.771	1.663	0.228	0.779
%RSD 21.83	20.16	27.59	19.32	31.53

Table 5.6. Discrete Mechanical Analysis of a Polymethacrylate Film containing 2.67%w/w Plasticiser and 2.0% Syloid.

Free-Film Composition

Excipient	%w/w	% solids
Eudragit RS30D	35.50	10.65
Eudragit RL30D	9.00	2.70
Citroflex 2	3.00	3.00
Syloid 244FP	4.00	4.00
Purified water BP to	100.00	-
		20.35

Intercept on Y $J_R + J_o$ ($x10^{-8}$ Pa^{-1})	Instantaneous Elastic Compliance J_o ($x10^{-8}$ Pa^{-1})	Time-dependent Elastic Compliance J_R ($x10^{-8}$ Pa^{-1})	Elastic Modulus Go $x10^7$(Pa)	Newtonian Viscosity no $x10^9$(Pa s)
4.405	3.205	1.200	3.120	23.948
7.370	5.093	2.277	1.963	11.658
6.408	3.453	2.955	2.895	16.983
5.652	4.452	1.200	2.246	27.047
7.323	5.197	2.126	1.924	12.327
7.696	5.859	1.837	1.707	12.514
7.869	5.954	1.915	1.679	13.837
5.517	3.946	1.571	2.534	19.458
9.267	6.930	2.337	1.443	12.219
5.191	3.622	1.569	2.761	20.748
n 10	10	10	10	10
x 6.670	4.768	1.899	2.227	17.074
SD 1.487	1.233	0.548	0.574	5.504
%RSD 22.30	25.87	28.84	25.80	32.23

Table 5.7. Discrete Mechanical Analysis of a Polymethacrylate Film containing 3.0%w/w Plasticiser and 4.0%w/w Syloid.

Free-Film Composition

Excipient	%w/w	% solids
Eudragit RS30D	35.50	10.65
Eudragit RL30D	9.00	2.70
Citroflex 2	2.67	2.67
Syloid 244FP	-	-
Purified water BP to	100.00	-
		16.02

Intercept on Y $J_R + J_o$ ($x10^{-8}$ Pa^{-1})	Instantaneous Elastic Compliance J_o ($x10^{-8}$ Pa^{-1})	Time-dependent Elastic Compliance J_R ($x10^{-8}$ Pa^{-1})	Elastic Modulus G_o $x10^7$(Pa)	Newtonian Viscosity n_o $x10^9$(Pa s)
9.628	4.339	5.289	2.305	2.774
5.267	1.809	3.458	5.528	2.801
14.847	4.548	10.299	2.199	0.779
12.073	2.326	9.747	4.300	1.413
6.671	2.095	4.576	4.773	2.679
5.184	1.879	3.305	5.322	3.461
6.207	1.858	4.349	5.383	2.399
7.742	2.399	5.343	4.170	1.980
n 8	8	8	8	8
x 8.452	2.657	5.796	4.248	2.286
SD 3.483	1.125	2.715	1.328	0.860
%RSD 41.21	42.35	46.85	31.26	37.63

Table 5.8. Discrete Mechanical Analysis of a Polymethacrylate Film containing 2.67%w/w Plasticiser.

Free-Film Composition

Excipient	%w/w	% solids
Eudragit RS30D	35.50	10.65
Eudragit RL30D	9.00	2.70
Citroflex 2	3.00	3.00
Syloid 244FP	-	-
Purified water BP to	100.00	-
		16.35

Intercept on Y $J_R + J_o$ ($x10^{-8}$ Pa^{-1})	Instantaneous Elastic Compliance J_o ($x10^{-8}$ Pa^{-1})	Time-dependent Elastic Compliance J_R ($x10^{-8}$ Pa^{-1})	Elastic Modulus G_o $x10^7$(Pa)	Newtonian Viscosity η_o $x10^9$(Pa s)
14.761	4.577	10.184	2.185	0.733
14.737	4.421	10.316	2.262	0.960
22.703	7.967	14.736	1.255	0.593
15.938	3.413	12.525	2.930	0.732
11.221	2.459	8.762	4.067	0.872
16.230	5.791	10.439	1.727	0.689
13.038	2.733	10.305	3.660	1.318
13.489	3.920	9.569	2.551	0.965
n 8	8	8	8	8
x 15.265	4.410	10.855	2.580	0.858
SD 3.420	1.790	1.894	0.944	0.228
%RSD 22.38	40.60	17.45	36.60	26.58

Table 5.9. Discrete Mechanical Analysis of a Polymethacrylate Film containing 3.0%w/w Plasticiser.

Free-Film Composition

Excipient	%w/w	% solids
Eudragit RS30D	35.50	10.65
Eudragit RL30D	9.00	2.70
Citroflex 2	1.34	1.34
Syloid 244FP	-	-
Purified water BP to	100.00	-
		14.69

Intercept on Y $J_R + J_o$ ($x10^{-8}$ Pa^{-1})	Instantaneous Elastic Compliance J_o ($x10^{-8}$ Pa^{-1})	Time-dependent Elastic Compliance J_R ($x10^{-8}$ Pa^{-1})	Elastic Modulus Go $x10^7$(Pa)	Newtonian Viscosity n_o $x10^9$(Pa s)
2.660	1.829	0.831	5.469	10.994
3.418	2.451	0.967	4.080	16.935
2.381	1.471	0.910	6.799	15.298
2.889	1.852	1.037	5.400	12.848
3.190	2.263	0.927	4.419	16.558
2.812	1.910	0.902	5.237	16.920
2.305	1.430	0.875	6.992	14.997
2.766	1.654	1.112	6.045	14.216
n 8	8	8	8	8
x 2.803	1.858	0.945	5.555	14.846
SD 0.375	0.375	0.091	1.032	2.106
%RSD 13.37	19.23	9.64	18.57	14.19

Table 5.10. Discrete Mechanical Analysis of a Polymethacrylate Film containing 1.34%w/w Plasticiser.

Free-Film Composition

Excipient	%w/w	% solids
Surelease Dispersion (25%w/w solids)	60.0	15.0
Purified water BP to	100.0	-
		15.0

Intercept on Y $J_R + J_o$ ($\times 10^{-8}$ Pa^{-1})	Instantaneous Elastic Compliance J_o ($\times 10^{-8}$ Pa^{-1})	Time-dependent Elastic Compliance J_R ($\times 10^{-8}$ Pa^{-1})	Elastic Modulus G_o $\times 10^7$ (Pa)	Newtonian Viscosity η_o $\times 10^9$ (Pa s)
22.868	21.361	1.507	0.468	3.150
26.090	23.596	2.494	0.424	2.416
24.824	22.857	1.967	0.438	3.768
24.014	22.224	1.790	0.450	4.098
18.928	17.210	1.718	0.581	5.053
21.214	19.838	1.376	0.504	2.856
19.853	15.416	4.437	0.649	5.952
23.069	20.197	2.872	0.495	4.250
n 8	8	8	8	8
x 22.608	20.338	2.270	0.501	3.943
SD 2.460	2.824	1.008	0.077	1.169
%RSD 10.88	13.89	44.41	15.45	29.64

Table 5.11. Discrete Mechanical Analysis of an Ethylcellulose (Surelease) Film.

Free-Film Composition

Excipient	%w/w	% solids
Silicone Emulsion X7-2837(A)	21.88	11.60
Colloidal Silica X7-2837(B)	34.10	5.80
Purified water BP to	100.00	-
		17.40

Intercept on Y $J_R + J_o$ ($x10^{-8}$ Pa^{-1})	Instantaneous Elastic Compliance J_o ($x10^{-8}$ Pa^{-1})	Time-dependent Elastic Compliance J_R ($x10^{-8}$ Pa^{-1})	Elastic Modulus G_o $x10^7$(Pa)	Newtonian Viscosity n_o $x10^9$(Pa s)
18.937	17.242	1.695	0.580	16.170
12.931	11.281	1.650	0.886	11.089
17.552	16.406	1.146	0.609	8.850
19.829	19.035	0.794	0.525	14.240
13.135	12.032	1.103	0.831	14.844
17.438	16.691	0.747	0.599	9.158
15.089	13.838	1.251	0.723	12.056
19.188	15.218	3.970	0.657	17.484
n 8	8	8	8	8
x 16.762	15.218	1.545	0.676	12.986
SD 2.719	2.667	1.039	0.127	3.199
%RSD 16.22	17.53	67.25	18.81	24.63

Table 5.12. Discrete Mechanical Analysis of a Silicone Elastomer Film containing Silicone Emulsion:Colloidal Silica 2:1.

Free-Film Composition

Excipient	%w/w	% solids
Silicone Emulsion X7-2837(A)	43.77	23.20
Colloidal Silica X7-2837(B)	34.12	5.80
Purified water BP to	100.00	-
		29.00

Intercept on Y $J_R + J_o$ ($x10^{-8}$ Pa^{-1})	Instantaneous Elastic Compliance J_o ($x10^{-8}$ Pa^{-1})	Time-dependent Elastic Compliance J_R ($x10^{-8}$ Pa^{-1})	Elastic Modulus G_o $x10^7$(Pa)	Newtonian Viscosity n_o $x10^9$(Pa s)
24.332	12.700	11.632	0.787	4.452
19.080	15.963	3.117	0.626	12.156
24.305	16.292	8.013	0.614	4.872
19.011	14.503	4.508	0.690	14.136
17.641	13.852	3.789	0.722	15.012
28.169	24.661	3.508	0.406	9.625
22.227	18.119	4.108	0.552	16.150
n 7	7	7	7	7
x 22.109	16.584	5.525	0.628	10.920
SD 3.769	3.978	3.147	0.125	4.762
%RSD 17.05	23.99	56.95	19.85	43.61

Table 5.13. Discrete Mechanical Analysis of a Silicone Elastomer Film containing Silicone Emulsion:Colloidal Silica 4:1.

Free-Film Composition

Excipient	%w/w	% solids
Silicone Emulsion X7-2837(A)	32.83	17.40
Colloidal Silica X7-2837(B)	17.06	2.90
Purified water BP to	100.00	-
		20.30

Intercept on Y $J_R + J_o$ ($x10^{-8}$ Pa^{-1})	Instantaneous Elastic Compliance J_o ($x10^{-8}$ Pa^{-1})	Time-dependent Elastic Compliance J_R ($x10^{-8}$ Pa^{-1})	Elastic Modulus G_o $x10^7$(Pa)	Newtonian Viscosity n_o $x10^9$(Pa s)
11.132	9.063	2.069	1.103	4.470
11.464	10.526	0.938	0.950	6.833
30.531	16.232	14.299	0.616	4.321
19.687	11.493	8.194	0.870	12.939
40.076	35.427	4.649	0.282	5.654
34.801	33.281	1.520	0.300	5.323
36.389	19.753	16.636	0.506	2.845
11.488	9.503	1.985	1.052	8.817
11.956	11.218	0.738	0.891	7.744
18.830	15.487	3.343	0.646	3.733
n 10	10	10	10	10
x 22.635	17.198	5.437	0.722	6.268
SD 11.654	9.658	5.749	0.297	2.980
%RSD 51.49	56.16	105.7	41.08	47.55

Table 5.14. Discrete Mechanical Analysis of a Silicone Elastomer Film containing Silicone Emulsion:Colloidal Silica 6:1.

5.3.3. Graphical presentation and interpretation of creep compliance data.

The formulations of the free-films studied may be classified into four groups according to the polymer type and the presence of plasticiser and other excipients within the films.

5.3.3.1. Effect of plasticiser concentration on the mechanical properties of films containing the polymethacrylates.

Figures 5.11 to 5.14 inclusive show the effect of the plasticiser (triethylcitrate) concentration on the mechanical properties of films prepared from aqueous dispersions of Eudragit RS30D and RL30D. Figure 5.11 clearly shows that an increase in the plasticiser concentration within such films results in an enhanced instantaneous elastic compliance. It is pertinent to note that concentrations of plasticiser in excess of 3%w/w resulted in films which were inherently sticky in nature and indeed even at this level, under the working temperature of the coating chamber, would cause problems of pellet agglomeration. For the purposes of studying the tensile properties of films as a consequence of plasticiser presence however, it was possible to prepare free-films containing 3%w/w triethylcitrate. A plasticiser concentration of 1.34%w/w (expressed as percent weight dry solids) was sufficient to enable complete film formation at approximately 43°C; quantities less than this however lead to problems in respect of the film forming temperature (see Chapter 3).

Polymethacrylate films of the same composition, as anticipated, also show an significant increase in the time-dependent elastic compliance with increasing percent plasticiser. The effect of plasticiser on the tensile properties of polymeric films is to increase the both the instantaneous and the time-dependent elastic component with a corresponding reduction in the brittleness of such films.

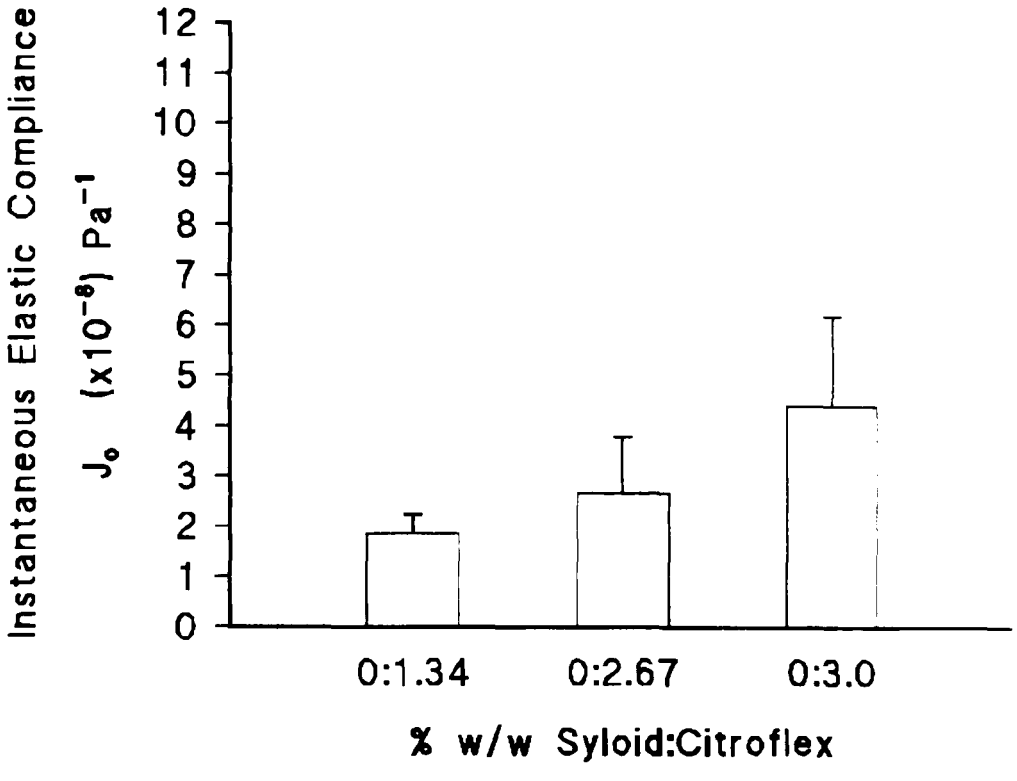


Figure 5.11. Instantaneous elastic compliance of free-films of the polymethacrylates as a consequence of plasticiser concentration.

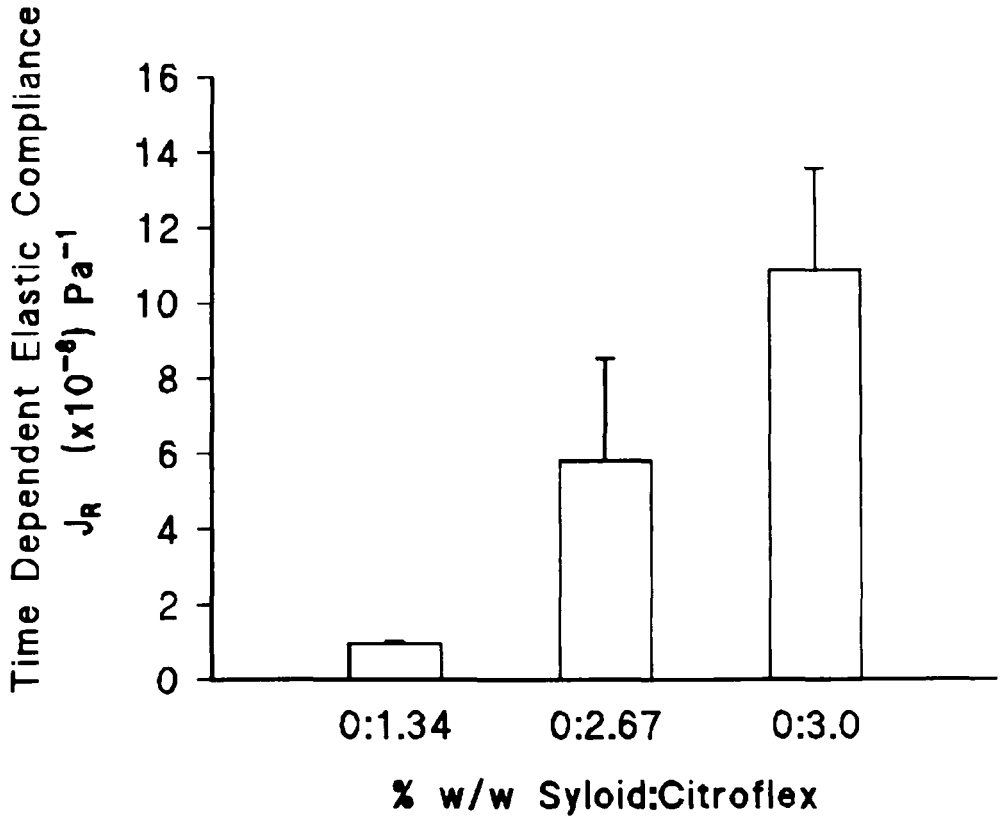


Figure 5.12. Time-dependent elastic compliance of free-films of the polymethacrylates as a consequence of plasticiser concentration.

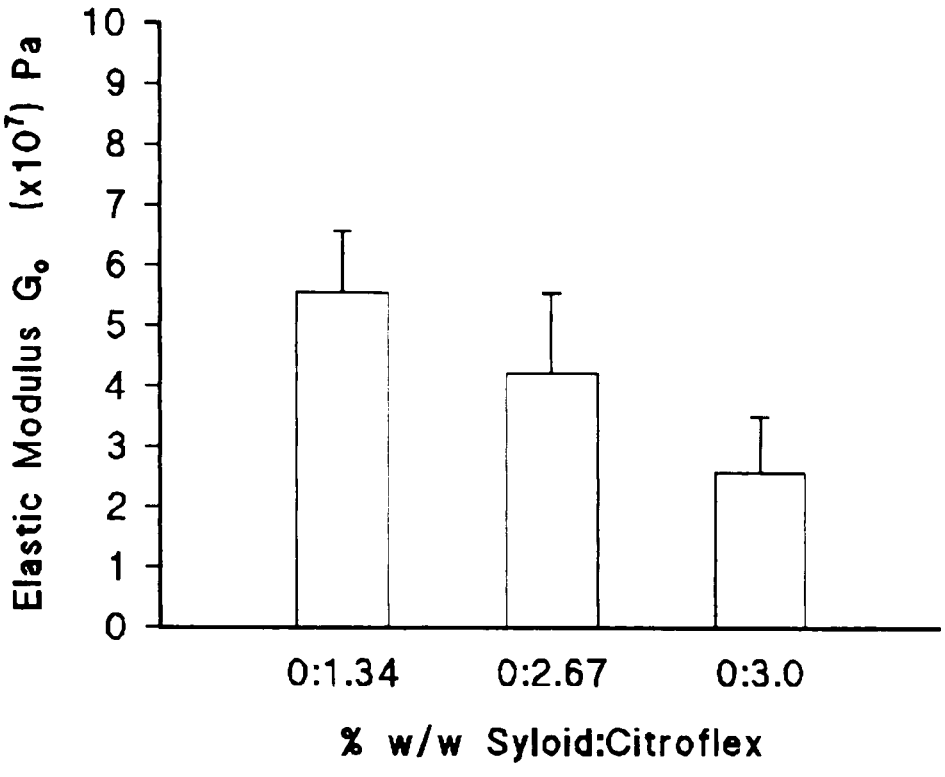


Figure 5.13. Elastic modulus of free-films of the polymethacrylates as a consequence of plasticiser concentration.

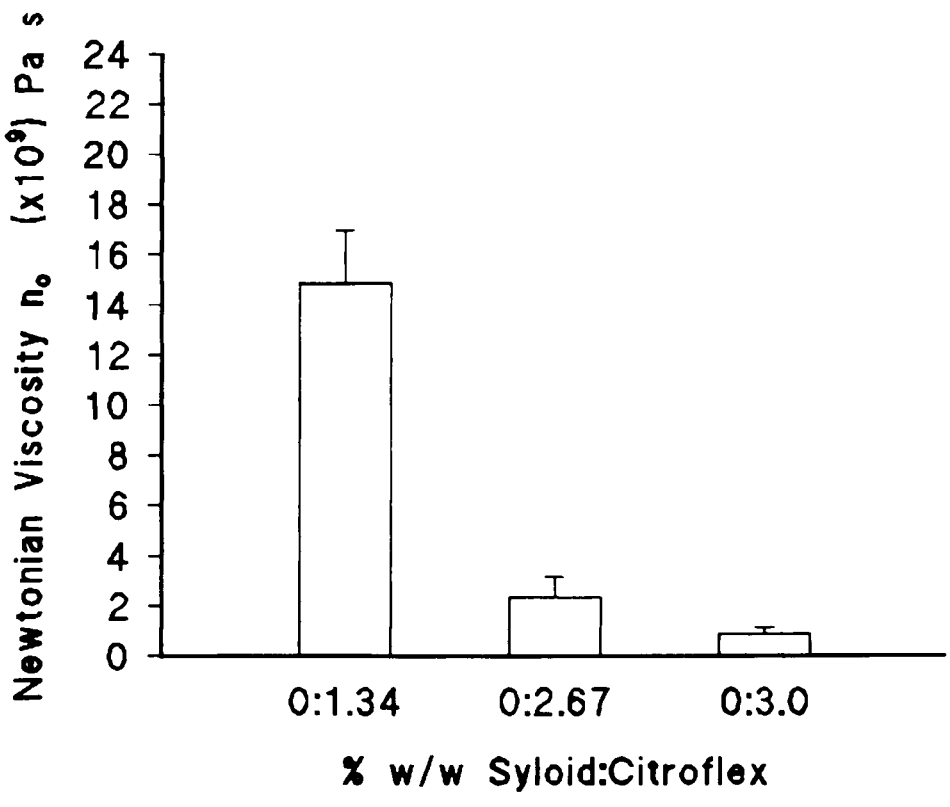


Figure 5.14. Newtonian viscosity of free-films of the polymethacrylates as a consequence of plasticiser concentration.

Since the elastic modulus G_0 is inversely proportional to the instantaneous elasticity J_0, it is not unreasonable to expect a reduction in G_0 with increased plasticiser concentration. One of the consequences of increasing the plasticiser concentration of a given polymer film is to enhance the elasticity of that film; this is reflected in a corresponding reduction in the elastic modulus G_0. This is confirmed by Figure 5.13 which shows that by increasing the proportion of triethylcitrate in the polymethacrylate film there is a corresponding reduction in the elastic modulus.

The Newtonian viscosity η_0 of a viscoelastic material is derived from the late linear region of time-dependent elastic region of the creep compliance profile for a material under constant applied stress. Equation 5.16 indicates that the apparent Newtonian viscosity is in fact inversely proportional to J_N, the non-recoverable viscous deformation. Hence a relatively low Newtonian viscosity is indicative of a relatively high non-recoverable viscous component. Figure 5.14 shows that with increasing plasticiser concentration for films containing the Eudragits, there is a reduction in the apparent Newtonian viscosity, but more importantly an increase in the non-recoverable elastic component of such films under applied stress. The viscous compliance J_N represents plastic deformation and arises when bonds are irreversibly broken and the initial structure becomes non-recoverable; this plastic deformation is permanent. In summary, increasing the plasticiser component of such films enhances plastic, non-recoverable deformation under applied stress.

5.3.3.2. Effect of Syloid concentration on the mechanical properties of polymethacrylate films with constant plasticiser concentration.

Figures 5.15 to 5.18 inclusive [each at constant plasticiser concentration of 2.67w/w (expressed as percent weight dry solids)], show the effect of the presence of Syloid 244FP on the mechanical properties

of free-films prepared from aqueous polymeric dispersions of Eudragit RS30D and RL30D. As previously discussed, the presence of Syloid (silicon dioxide) was a necessity in these polymethacrylate formulations in order to prevent pellet agglomeration and adherence of spheres to the coating chamber wall during the application of the dispersion. There are however associated problems as highlighted by these results. Zero or inadequate levels of this excipient result in very sticky films, even at room temperature. At 40 to 45°C these films are exceptionally sticky and it was not possible to coat pellets with polymethacrylate aqueous dispersions without this excipient as a component of the aqueous dispersion formulation.

Interestingly, Figure 5.15 shows that the relationship between the instantaneous elastic compliance and the concentration and presence of Syloid in the film is not linear. Films containing 0% and 4% w/w Syloid show a significantly lower instantaneous elastic component than those containing 2%w/w Syloid. For films displaying a high instantaneous elastic component, one might at this stage anticipate problems which may arise as a consequence of compression of pellets coated with these formulations, since on removal of the force provided by the compression process, one might postulate that the instantaneous elastic recovery may be so great as to prevent the formation of a tablet of sound mechanical properties, in particular friability and diametral crushing strength.

The situation is slightly different when consideration is made of the time-dependent compliance J_R (Figure 5.16). Those films containing the relatively high Syloid concentration of 4%w/w, exhibit a lower time dependent elastic component than those containing 0 and 2%w/w.

The elastic modulus G_o (being a reciprocal of the instantaneous elasticity J_o) of the film containing 4%w/w Syloid is higher than that containing 2% and lower than G_o for films containing 0%w/w silicon dioxide (Figure 5.17). For a series of polymethacrylate films containing

constant plasticiser content (Figure 5.17): with 0%w/w silicon dioxide concentration the film was exceptionally sticky even under standard conditions of room temperature (reflected by the relatively high elastic modulus); with 2%w/w silicon dioxide the film displayed the greatest elasticity, both instantaneous and time-dependent and this is supported by a relatively low elastic modulus; at 4%w/w silicon dioxide the film exhibited a relatively low time-dependent elastic component (Figure 5.16) (again this is reflected in the elastic modulus value determined for this film).

Of tremendous importance and interest are the apparent Newtonian viscosity values (Figure 5.18). The 4%w/w-Syloid containing film exhibits a significantly greater apparent Newtonian viscosity than the other two film formulations; this is indicative of a reduced non-recoverable elastic tendency on the application of load.

For the three films formulations represented in these figures therefore, least permanent and non-recoverable damage is caused to that film containing 4%w/w Syloid than for those containing 2%w/w and 0%w/w Syloid. At these latter Syloid concentrations there is greater tendency for permanent, non-recoverable, plastic deformation under applied stress. This parameter is of tremendous importance when selecting a suitable polymeric film composition, for application to pellets which are to be subjected to compression into tablets and for which film coat damage is to be prevented at best, or minimised at worst.

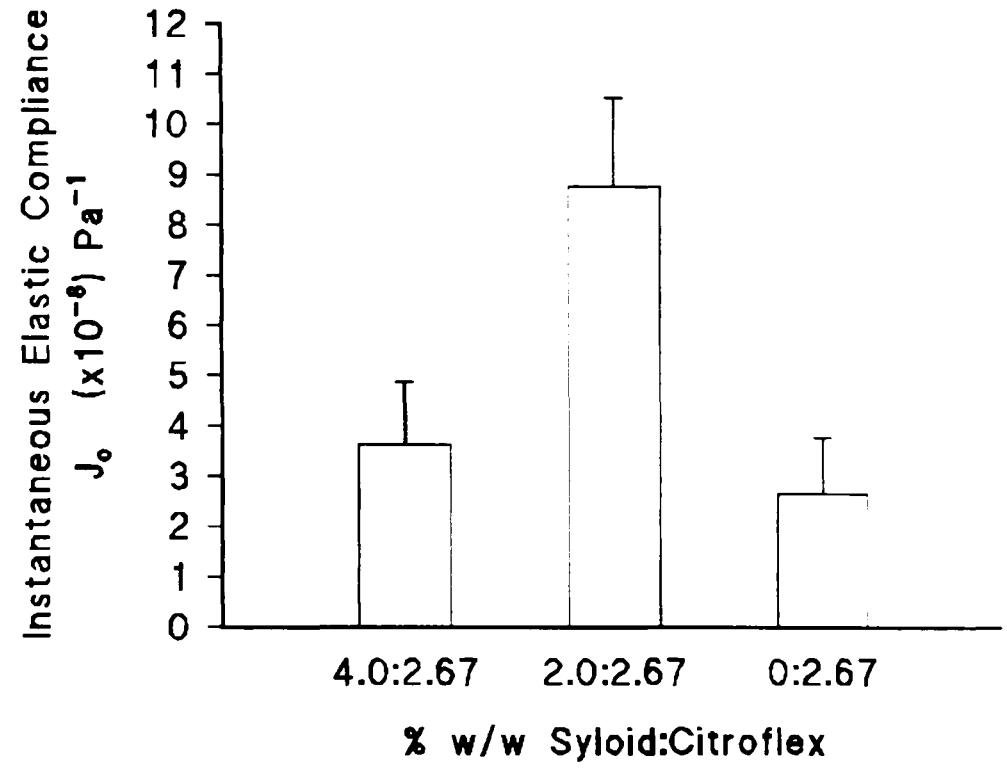


Figure 5.15. Instantaneous elastic compliance of free-films of the polymethacrylates as a consequence of the presence and concentration of Syloid 244FP.

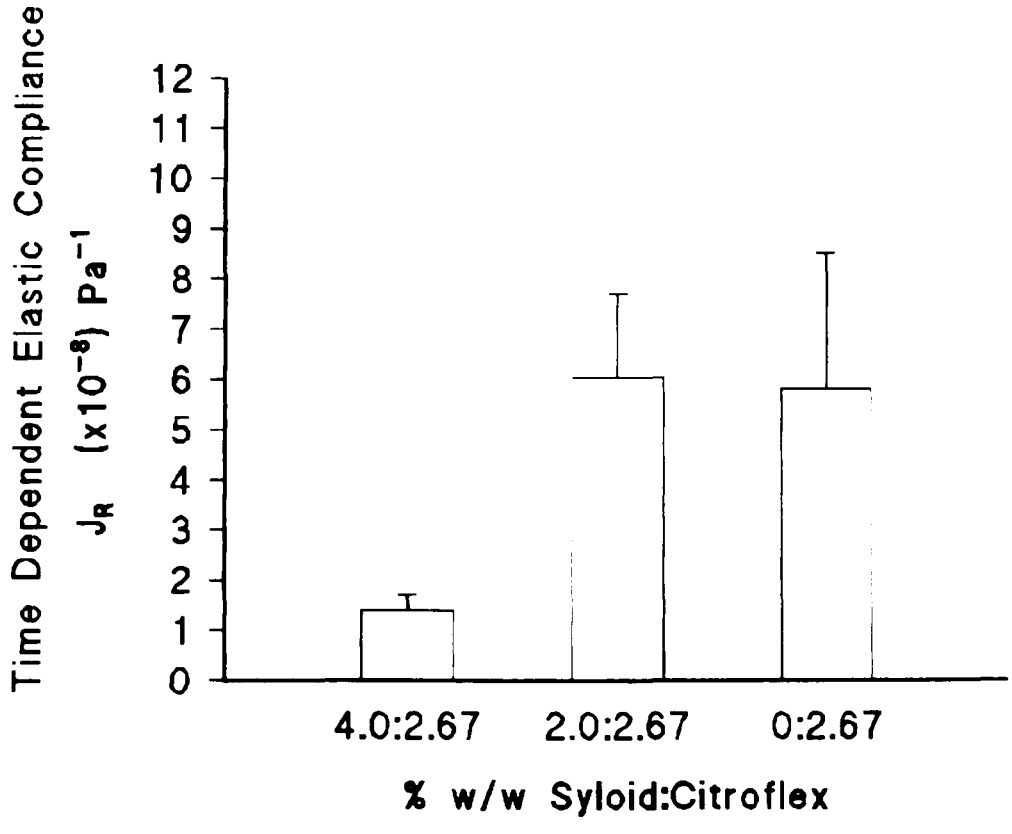


Figure 5.16. Time-dependent elastic compliance of free-films of the polymethacrylates as a consequence of the presence and concentration of Syloid 244FP.

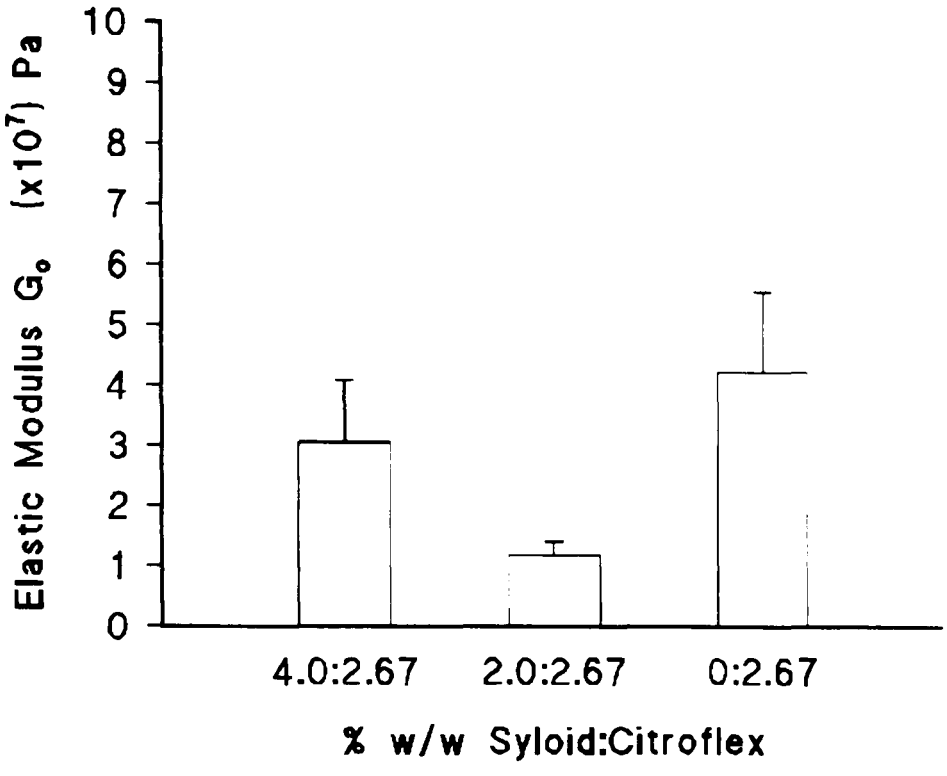


Figure 5.17. Elastic modulus of free-films of the polymethacrylates as a consequence of the presence and concentration of Syloid 244FP.

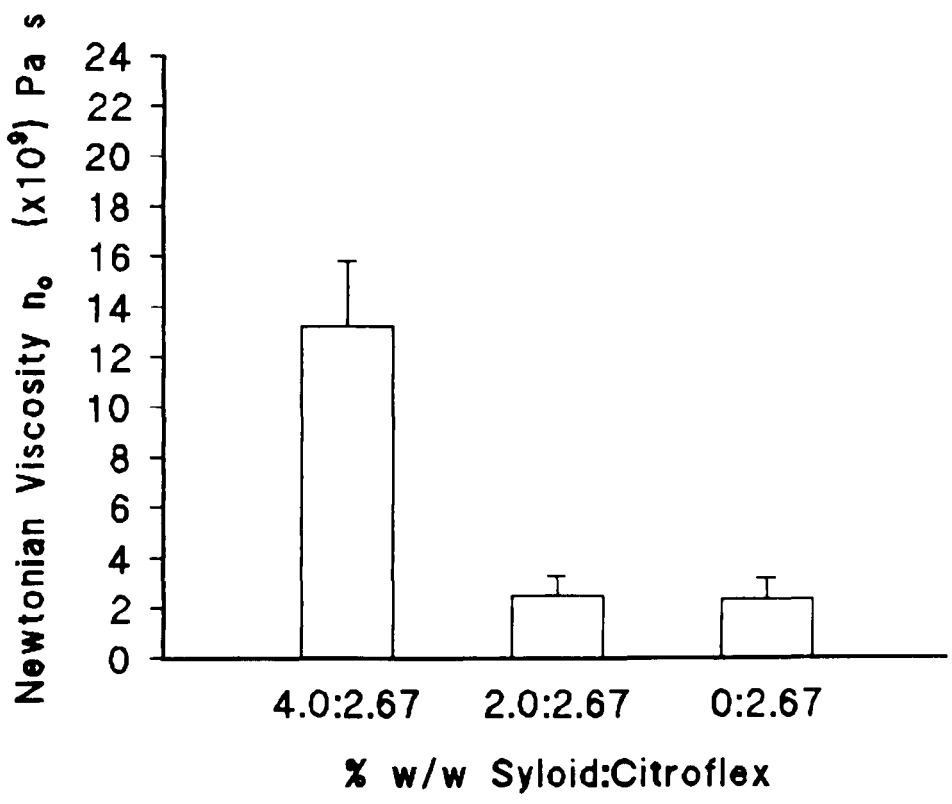


Figure 5.18. Newtonian viscosity of free-films of the polymethacrylates as a consequence of the presence and concentration of Syloid 244FP.

5.3.3.3. An overview of the effect of the presence and concentration of plasticiser and Syloid on the mechanical properties of free-films containing the polymethacrylates.

Figures 5.19 to 5.22 summarise the effect of the presence and concentration of both triethylcitrate and Syloid 244FP in free-film Eudragit formulations prepared using the rotating PTFE cylinder technique described previously (section 5.2.2).

Figure 5.19 illustrates that the effect of plasticiser concentration on the instantaneous elastic compliance is less significant than the presence and concentration of other excipients, notably in this situation, Syloid 244FP. A decrease in the Syloid concentration or an increase in the plasticiser concentration in films composed of the polymethacrylates has the effect of increasing the time-dependent elastic compliance of these free-films (Figure 5.20).

Figure 5.21 illustrates the fact that the presence and concentration of adjuvents in polymeric film formulations has a significant influence on the elastic modulus G_0 of free-films. Indeed the presence of additional excipients within the composition of the film may make a major contribution to the mechanical properties, as well as to the processing conditions during film application, reasons for which these additional components were originally incorporated. Figure 5.22 shows that at high plasticiser concentration (3%w/w triethylcitrate) the apparent Newtonian viscosity is relatively high (17.074×10^9 Pa s) and it may therefore be concluded that there is a correspondingly low non-recoverable elastic deformation associated with these films under stress. Low or zero Syloid concentrations result in films exhibiting low apparent Newtonian viscosities and a correspondingly relatively high tendency for plastic, permanent deformation under the application of stress. These films are however relatively less brittle (at constant plasticiser concentrations) than those films with a high Syloid content.

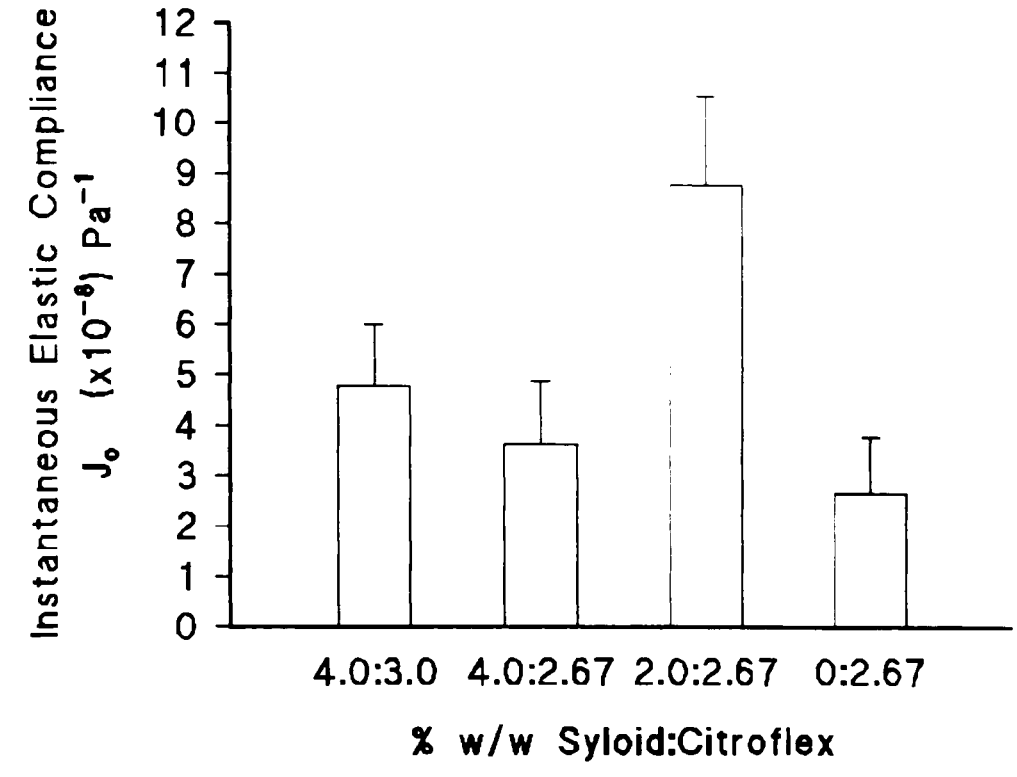


Figure 5.19. Cumulative effect of plasticiser and Syloid concentrations on the instantaneous elastic compliance of free-films composed of the polymethacrylates.

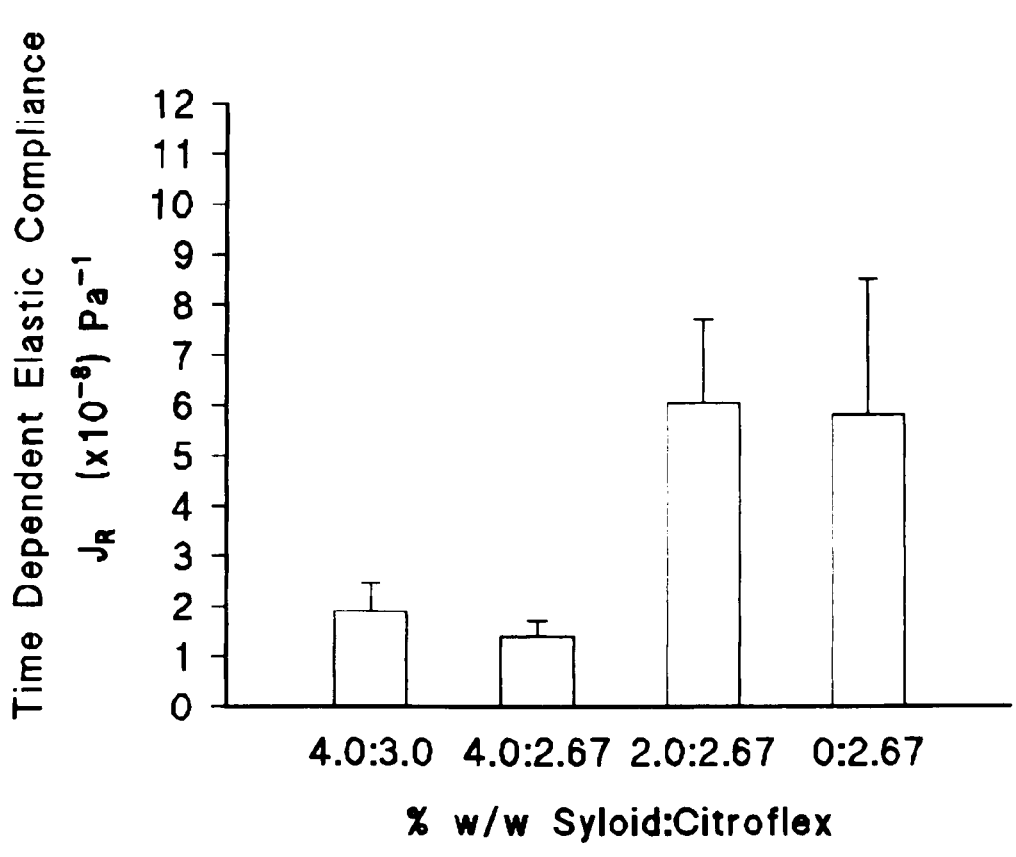


Figure 5.20. Cumulative effect of plasticiser and Syloid concentrations on the time-dependent elastic compliance of free-films composed of the polymethacrylates.

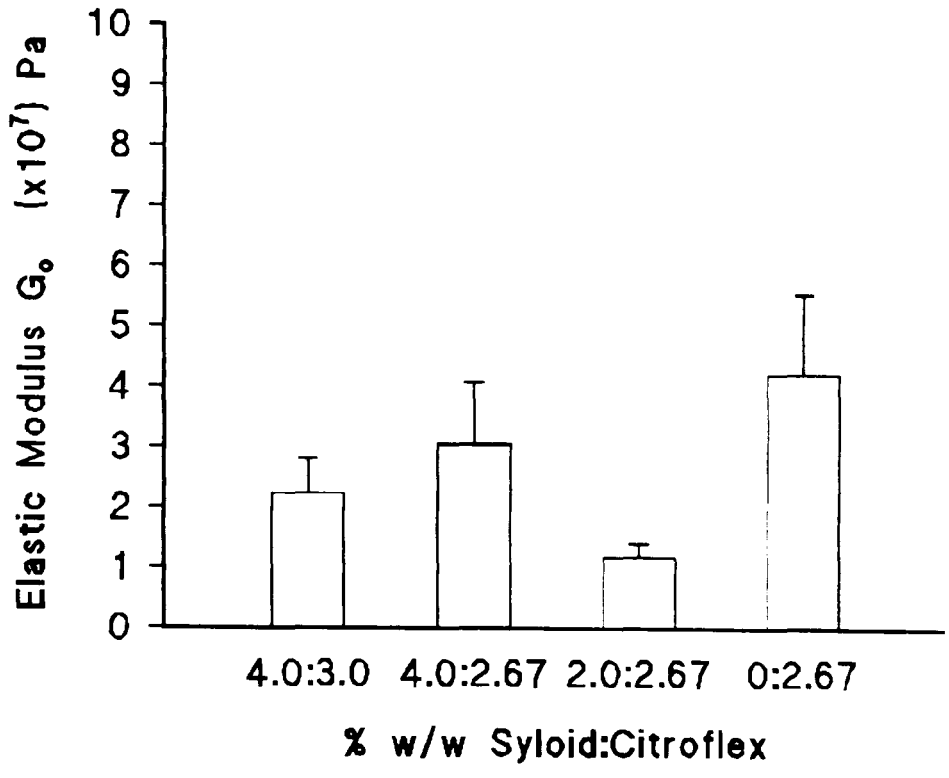


Figure 5.21. Cumulative effect of plasticiser and Syloid concentrations on the elastic modulus of free-films composed of the polymethacrylates.

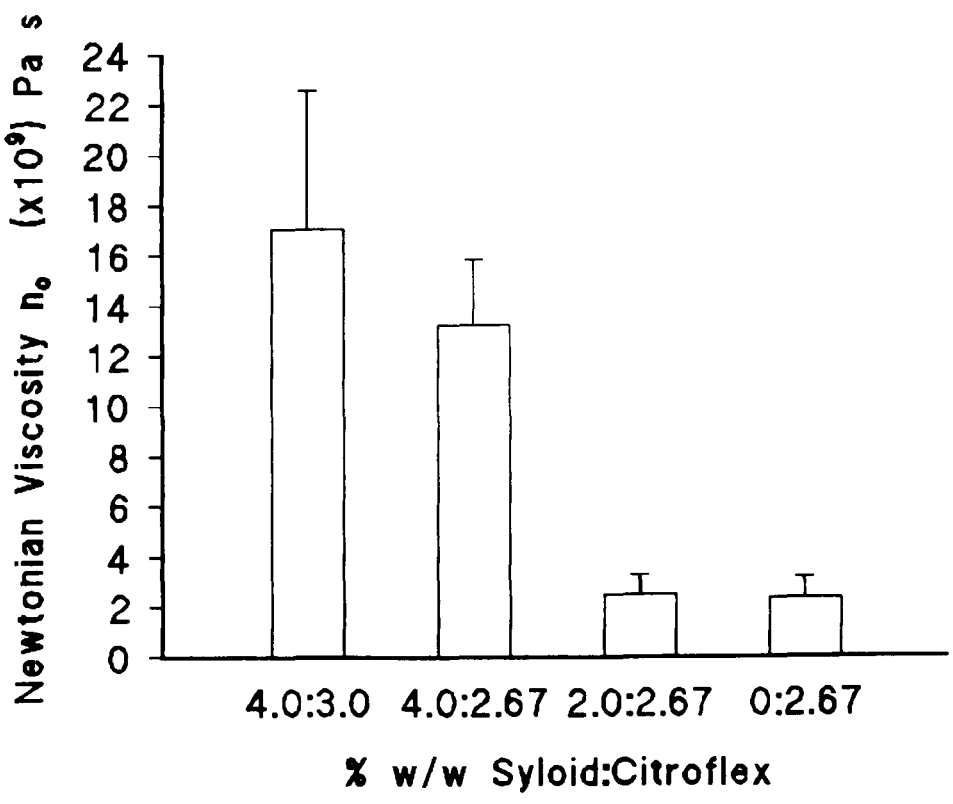


Figure 5.22. Cumulative effect of plasticiser and Syloid concentrations on the Newtonian viscosity of free-films composed of the polymethacrylates.

A film containing 0% Syloid and 2.67%w/w triethylcitrate exhibits a degree of tackiness and stickiness; this becomes less of a problem with a increasing Syloid concentration. At 4%w/w Syloid there is no tackiness associated with either the free-film or that applied to pellets using the fluidised bed apparatus and technique described previously.

5.3.3.4. Effect of the polymer on the mechanical properties of free-films.

Figures 5.23 to 5.26 inclusive give an overview of the mechanical properties of those films applied as aqueous polymeric dispersions to ibuprofen pellets.

Figure 5.23 shows that the Silicone Elastomer formulations and the Surelease (ethylcellulose) film exhibit an extremely high instantaneous elastic compliance. With increasing silicone to silica ratio in the Silicone Elastomer formulations there is a corresponding increase in the instantaneous elastic component; there are also problems with these films associated with the high instantaneous elastic recovery and thus a greater susceptibility of these films to environmental conditions. Any environmental vibrations, however small, have a deleterious effect on the quality of the data obtained; this is in fact illustrated by the large error bars associated with the data exposed graphically in Figures 5.23 and 5.24. Also, in order to achieve a film penetration of less than 6 micrometers, it was necessary to use an indenting load of 0.5g for the elastomer films composed of silicone to silica ratios of greater than 2:1. These formulations are exceptionally sensitive to applied stress; this is reflected in the instantaneous and the time-dependent elastic compliance data. The polymethacrylate formulation shown in these figures is that containing 2.67%w/w triethylcitrate and 4%w/w Syloid. This Eudragit formulation represents that film formulation which was applied to pellets which were subsequently compressed satisfactorily.

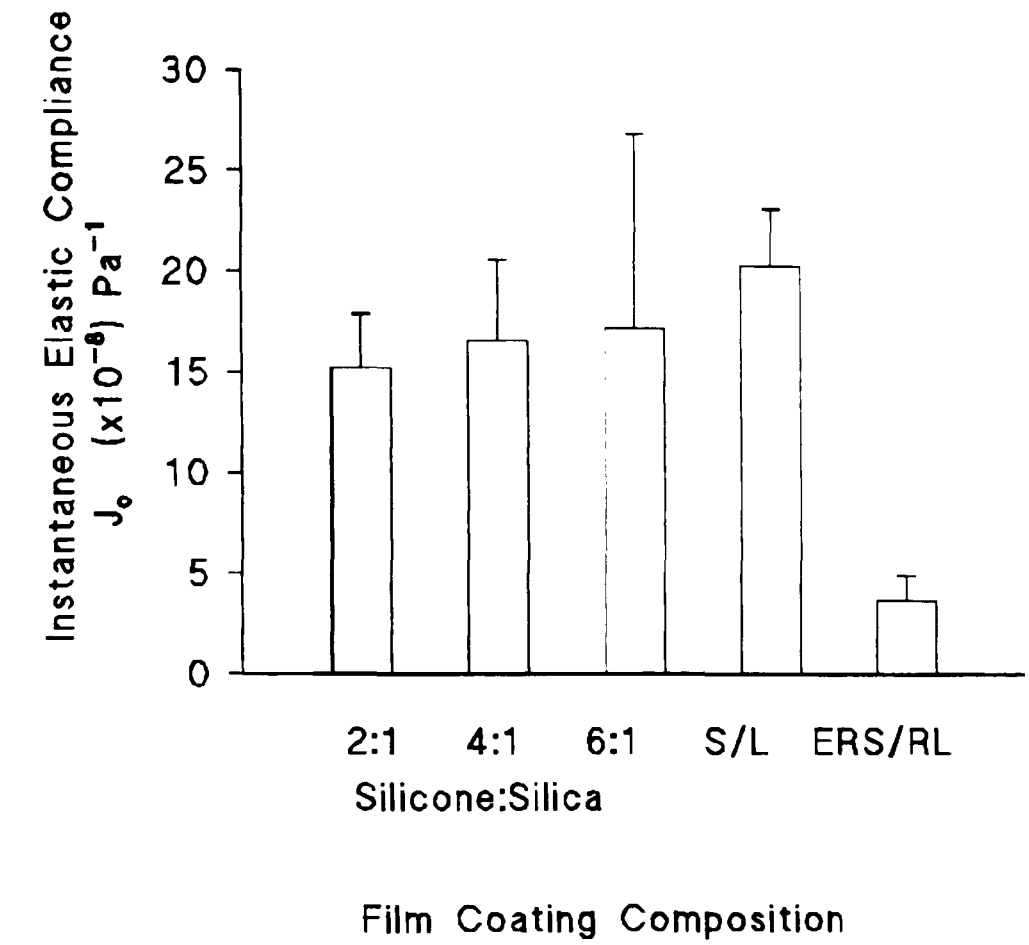


Figure 5.23. Instantaneous elastic compliance of free-films as a consequence of polymer type.

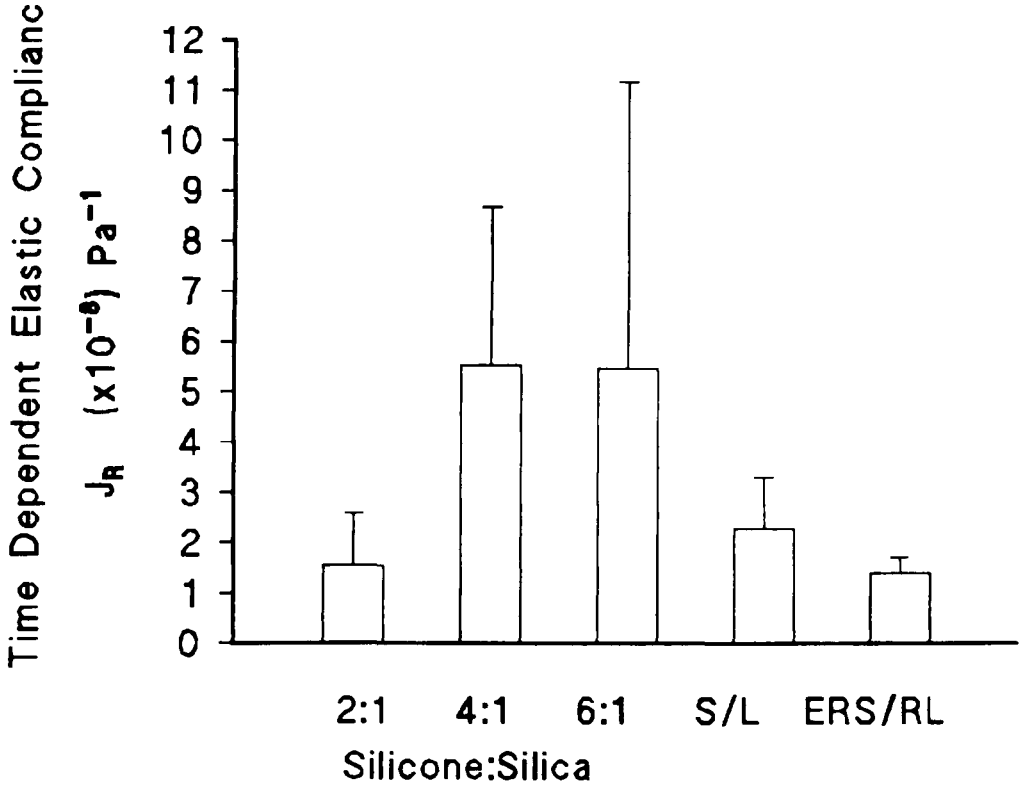


Figure 5.24. Time-dependent elastic compliance of free-films as a consequence of polymer type.

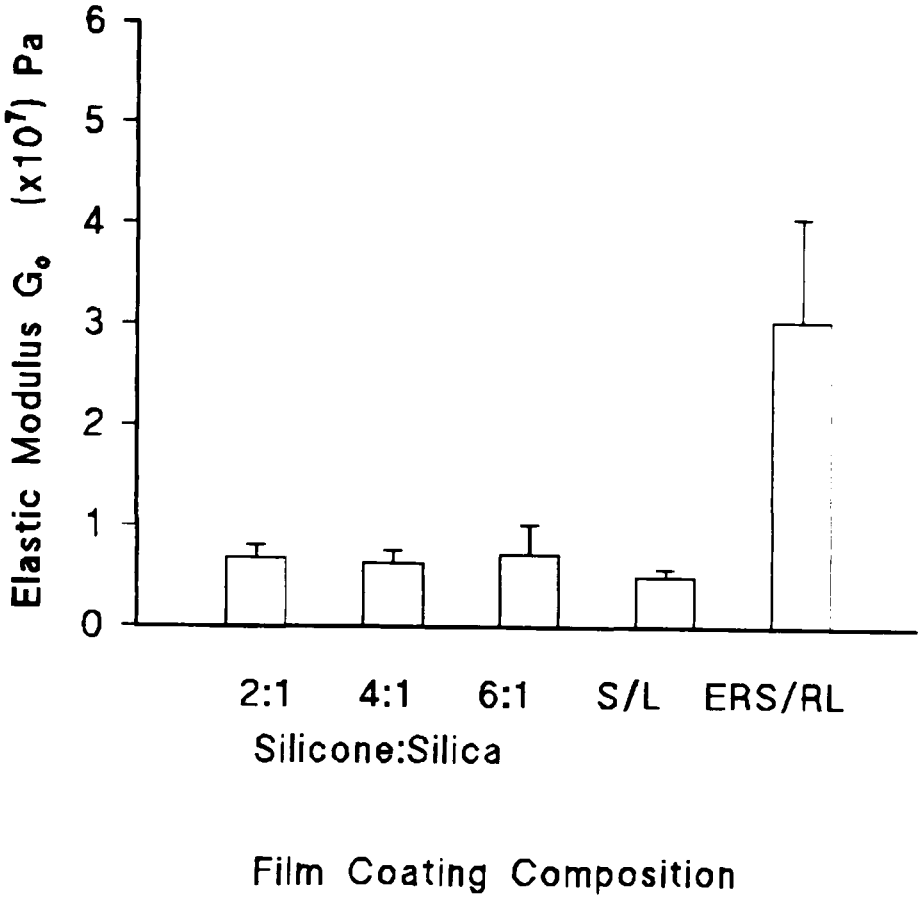


Figure 5.25. Elastic modulus of free-films as a consequence of polymer type.

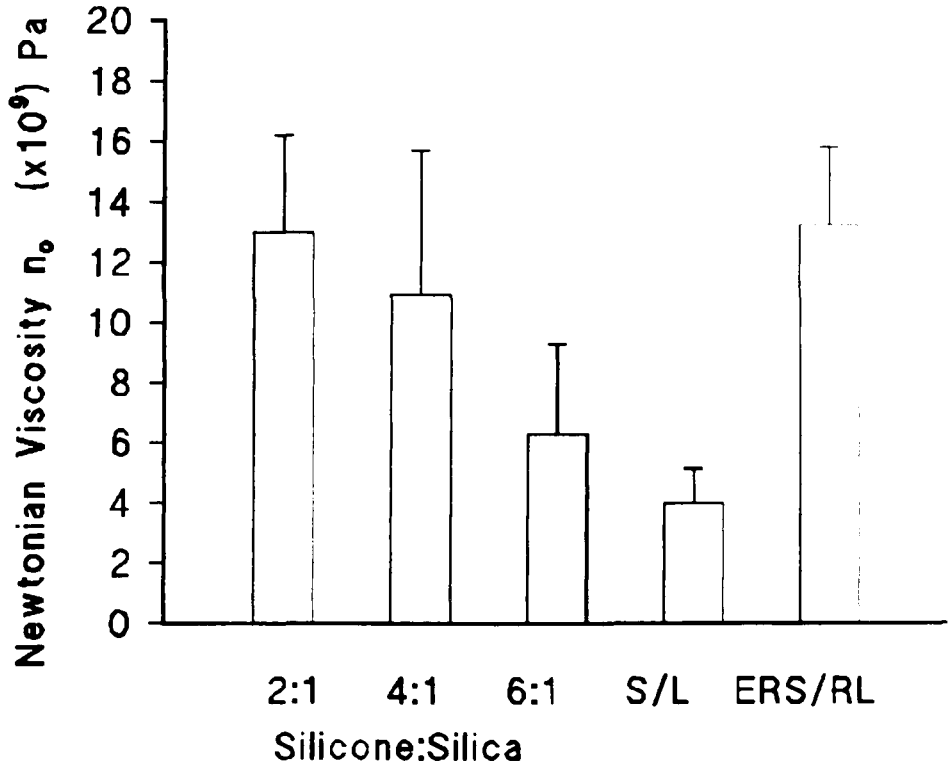


Figure 5.26. Newtonian viscosity of free-films as a consequence of polymer type.

Consideration of Figures 5.23, 5.24 and 5.25 yields information relating to those film properties necessary to withstand applied stress associated with pellet compression. The integrity of both the polymeric membrane and the pellet cores must remain intact in spite of the compression process.

Pellets coated with the Silicone Elastomer films were not compressible; reasons for this are discussed in detail in Chapter 7 (section 7.3). Briefly, the Silicone Elastomer coated pellets achieved such an instantaneous elastic recovery following release from the punches and die that they collapsed immediately into a mass resembling that blend from which the tablets were intended to be composed. This scenario occurred even under extreme compaction pressures; details of which are given in section 7.2. Reasons for this appear to be attributable to the high instantaneous and time-dependent elastic components exhibited by these films. Initially, on selecting potential aqueous polymeric release retarding dispersions, it was postulated that those systems exhibiting a high degree of elasticity may be those affording the greatest protection to pellets on compression. These results however indicate that those polymers displaying relatively high elastic tendencies, have associated problems in respect of instantaneous recovery on removal of the applied stress.

The Surelease (ethylcellulose) film, as illustrated by Figure 5.23, exhibits high instantaneous elastic deformation and recovery; this polymer actually displayed the greatest instantaneous elasticity of any formulation studied (20.34×10^{-8} Pa^{-1}). Its time-dependent component, although greater than the polymethacrylate film and the Silicone Elastomer film (2:1), was considerably less than that exhibited by the 4:1 and the 6:1 elastomer formulations. Unfortunately, Surelease-coated pellets exhibited a tendency towards sticking during the coating process, although careful optimisation of the coating conditions facilitated a

satisfactory coating process. Disadvantages of the Surelease aqueous formulation however were further compounded by the fact that it was necessary to overcoat the polymer film with a film of Opadry (composed of HPMC, PEG 400 and PEG 6000). "The overcoat formulation is necessary to prevent the phenomenon of blocking (pellets loosely adhering to one another) after the coating process. The resulting clumps of pellets may cause inconsistent film thickness which could contribute to variable release rates" (Surelease product literature, Colorcon, 1985).

In summary, Surelease films exhibit a high degree of elasticity, the greatest component being instantaneous rather than time-dependent, on the application of stress. Surelease films therefore have a lower elastic modulus (Figure 5.25) and they also exhibit the lowest Newtonian viscosity (Figure 5.26) of all the formulations studied. In line with this low Newtonian viscosity, as a consequence of the relationship between this parameter and non-recoverable plastic deformation, the Surelease film is therefore most susceptible to permanent non-recoverable damage under applied stress.

5.4. Conclusions.

Indentation hardness testing provides a valuable means of assessing the tensile properties of polymeric films.

The analysis of elastic and plastic deformation of polymer films induced by an indenter tip is however influenced by a number of parameters. Films must be of uniform thickness, free from entrapped air, of uniform surface characteristics and samples must be large enough such that each indentation occurs on a fresh area of film. The effect of environmental conditions on the microindenter must also be carefully controlled. Any surface vibrations or air disturbance will have a considerable effect of the quality of the data obtained, in particular for those films which are extremely elastic and are therefore sensitive

to applied stress. All of these variables were carefully controlled during the quantitative evaluation of these films.

It was considered that although such a technique is influenced by a variety of factors, that indentation testing does provide a valuable means of evaluating the mechanical properties of polymers and the effect of the presence of other excipients within the polymeric film. This technique is of particular value within the scope of this work, whereby polymer coated pellets are subjected to applied stress by means of compression into tablets.

Valuable parameters which may be quantified using this technique of particular interest and usefulness in respect of this work include the instantaneous and time-dependent elastic deformation and recovery, the elastic modulus and the Newtonian viscosity.

The apparent Newtonian viscosity of a film gives an insight into how the polymer behaves under applied stress and is associated with the compliance of non-recoverable deformation. It is obtained from the late linear region of the creep compliance curve (Figure 5.6). The Newtonian viscosity of a material is inversely proportional to the non-recoverable viscous deformation (Equation 5.16). Hence a film exhibiting a large non-recoverable viscous deformation on the application of stress, will have a correspondingly low apparent Newtonian viscosity.

The instantaneous elastic compliance of a material is the reciprocal of the elastic modulus. Those materials displaying a relatively high instantaneous elastic component will therefore exhibit a relatively low elastic modulus.

In a given polymeric film formation the effect of increasing the plasticiser content, is to enhance the instantaneous and the time-dependent elastic components; there is a corresponding decrease in the elastic modulus and the apparent Newtonian viscosity. That is to say that the permanent non-recoverable plastic deformation associated with

applied stress, increases with increasing plasticiser concentration.

The presence of other excipients within a polymeric film other than the polymer itself and the plasticiser may also exhibit a considerable influence on the mechanical properties of a given polymeric film formulation. In this work, the presence of silicon dioxide within the polymethacrylate film has a tremendous influence on the mechanical properties of such a system. These effects are product specific and it is not feasible to make generalisations regarding the influence of these additional components on the resultant mechanical properties of films containing such excipients. Suffice to state that a consequence of the addition of silicon dioxide to polymethacrylate films is a significant influence on the elastic parameters and that the effect is concentration dependent.

It is evident from this study of the mechanical properties of polymeric films, in conjunction with the study discussed in Chapter 7 regarding the effect of compression on tablet formulation and pellet core and film coat integrity, that polymeric films exhibiting a relatively high elastic compliance, both instantaneous and time-dependent (Silicone Elastomer films with a high silica to silicone ratio and also Surelease films) are unlikely to satisfy the requirements for favourable tablet preparation due to this associated elastic recovery occurring immediately on removal of the applied stress.

It may also be concluded that those films exhibiting a relatively high elastic modulus (polymethacrylate films) and a relatively high apparent Newtonian viscosity (polymethacrylate films and Silicone Elastomer films containing a low silicone to silica ratio) provide greatest protection to the pellet core and to the film coat on pellet compression.

Within the scope of this work, of those aqueous polymeric film coating systems evaluated, the polymethacrylate (Eudragit) dispersion

appeared to form a more favourable film suitable for coating ibuprofen pellets, which must be able to withstand compression into tablets.

The effect of the compression process on the ability of coated pellets to withstand applied stress and the effect on the integrity of the film coat and the pellet core is discussed in Chapter 7.

It was considered necessary not only to evaluate and quantify the tensile properties of polymers as free-films but also to study the tensile properties of the pellet core and the polymeric membrane in-situ, since the process of pellet compaction involves the application of stress to polymer coated pellet cores. Chapter 6 is a study of the mechanical properties of uncoated and coated pellets. Using a Single Particle Crushing Assembly (Figure 6.4) the force required to cause single pellet fracture and the particle displacement under applied load were quantified. Yielding this information facilitated calculation of the tensile stress, per cent strain and work done in causing pellet fracture for the various formulations. Calculation of the elastic modulus of these discrete units was therefore made possible having quantified these parameters.

It was postulated that by gaining an insight into the tensile properties of these coated pellet formulations that it would be possible to design a compacted pellet tablet formulation in which the compression process had minimal effect on the integrity of pellet cores, the polymeric membrane and as a consequence, the drug release mechanism from these multiparticulates.

CHAPTER 6

A STUDY OF THE MECHANICAL PROPERTIES OF UNCOATED AND COATED PELLETS

6.1. Introduction.

As tabletting excipients and processing variables affect the physical strength of granules and tablets, so these factors affect the mechanical strength and tensile properties of pellets.

6.1.1. Mechanism of particle fracture.

Particles must be stressed in order that fracture is produced. When stress (force per unit area) is applied to a solid, the solid undergoes strain (ratio of change in a given dimension to its original value). An elastic material deforms under stress but returns to its original shape when the stress is removed. Hooke's Law states that stress is directly proportional to strain; the ratio of stress to strain gives the elastic modulus of that material. If a particle is stressed to too great an extent, failure occurs and the solid fractures at a stress known as the tensile strength. The behaviour of a plastic material is shown in Figure 6.1.

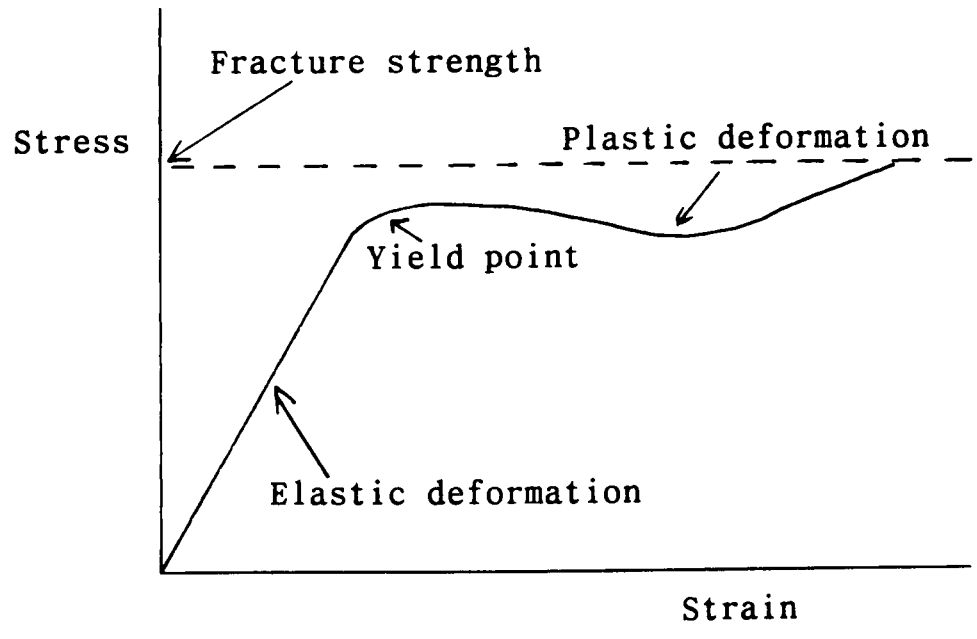


Figure 6.1. Stress-strain curve for a plastic material.

Initially within the elastic limit of the particle, the stress is proportional to the strain according to Hooke's Law. As the stress is increased, the elastic limit of the material is exceeded and at the yield

point and permanent deformation occurs. With the application of further stress, within the region of irreversible plastic deformation, the stress-strain curve is non-linear. As the stress is yet further increased particle fracture occurs.

When the application and release of stress causes permanent deformation, energy is expanded and cracks will be initiated in the solid. The furthest extension of a crack is the point of greatest stress. As real particles have irregular surfaces, the force is initially applied to the higher portions of the surface and consequently high stresses and temperatures exist locally. As fracture occurs, the points of application of force shift. Stress waves caused by the initial fracture release energy producing other regions of high stress from which new cracks or fracture may occur (Swarbrick and Boylan, 1990).

A "perfect" particle is composed of planes of molecules or ions which are separated by equal intermolecular attractive forces. When stress is applied, the intermolecular bonds may be stretched, but any molecule still has a balance of forces on it. However Figure 6.2 shows that movement away from the non-stressed equilibrium against attractive forces requires additional energy and the solid reaches equilibrium at a higher energy state (stored strain energy). The maximum attractive force that the solid can exert on the surface layer is the inflection point of the potential energy curve (Figure 6.2).

An external force in excess of this maximum causes an imbalance of forces and acceleration of one plane of molecules away from another. The "perfect" particle would then disintegrate into individual units. A real particle however fractures under less force than a "perfect" particle into a few relatively large particles and a number of fine particles with relatively few particles of intermediate size.

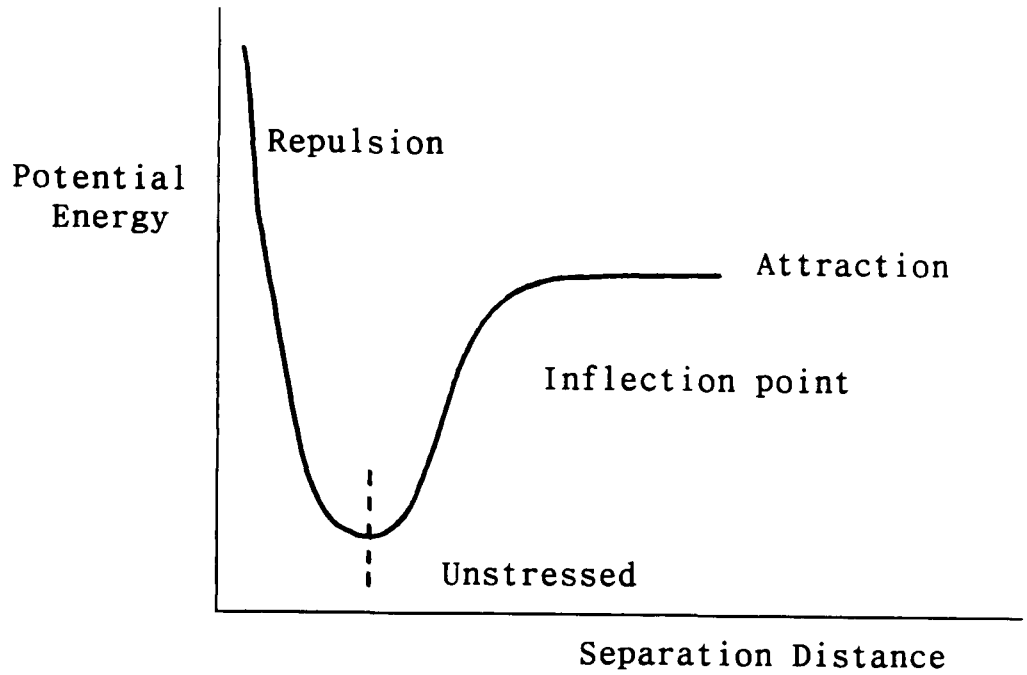


Figure 6.2. Diagrammatic illustration of the total potential energy against distance of separation.

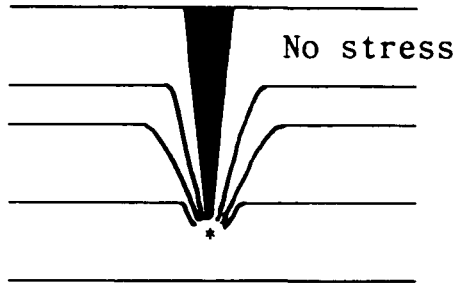


Figure 6.3. Crack concept and effect of radius of curvature (Swarbrick and Boylan, 1990).

It is postulated that the size of the large particles is related to the mechanism causing pellet fracture and that the size of the finer particles is related to the structure of the components from which these particles are composed. The presence of flaws or cracks leads to areas of weakness; damage would occur at these areas under lower stress than for a "perfect" particle. Stress concentrates in the region with maximum

curvature or the smallest radius of curvature (Figure 6.3). The stress intensifies as the length of the crack is increased and the crack becomes narrower. The tensile strength of a particle is significantly affected by the presence of cracks and flaws, since as the crack progresses on the application of stress, extra energy becomes available to accelerate the crack tip, the system becomes unstable and the crack progresses at high velocity.

The bulk stress does not have to be sufficient to break all the bonding forces "simultaneously" because only the bonds about the crack tip are breaking at any instant. The presence of many flaws close together will further reduce the tensile strength.

Plastic materials deform due to the sliding of planes of the solid over one another caused by the movement of dislocations under stress. In plastic behaviour the intermolecular forces between planes are not all broken at once; only enough bonds are broken to enable the dislocations to move to another position. Bonds reform behind the dislocation. This process continues leading to the slip of one plane over another. When plastic yield has occurred, the plastic slip may cause part of the solid to act as a wedge, creating tensile forces which may then propagate brittle fracture. In addition, the movement of dislocations may accumulate dislocations at a grain boundary, leading to the formation of a small hole.

Plastic materials are generally stronger than brittle materials; however once fracture is initiated the energy may decrease as the crack moves at high velocity in relation to the movement of dislocations and conferred plasticity.

Brittle fracture is essentially temperature independent, whereas plastic materials decrease in strength as the temperature is increased due to the greater mobility of dislocations. For a brittle material, a smaller particle has less of a probability of having a large flaw and

will be relatively stronger than a larger particle with more flaws. The rate of stress application is more crucial with plastic materials than brittle materials, since a fast rate of stress will cause brittle fracture, whereas a slow rate of stress application may provide time for plastic behaviour.

Bemrose and Bridgwater (1987) state that all particles contain weaknesses in the form of micro-cracks or cracks and that all normal particle structures will contain imperfections, dislocations and impurities. This, the authors claim, leads to non-uniform mechanical behaviour in the deformation or compression and subsequent fracture of particles. Bemrose and Bridgwater also state that the breakage strength of particles increases markedly as the diameter decreases since the size of the flaws and micro-cracks becomes smaller at smaller particle sizes.

6.1.2. Review of particle crushing techniques.

Techniques reported to date for measuring the mechanical strength of particles are varied and range from simply crushing granules with a spatula to more sophisticated apparatus.

Harwood and Pilpel (1968) describe a simple technique involving measuring that weight of lead shot necessary to crush granules of Griseofulvin. They showed a linear relationship between breaking load and surface area of granules. These authors and others report a considerable degree of scatter in considering any relationship between granule strength and size, however expressed. Ganderton and Selkirk (1970) used a spatula to ascertain the crushing strength of granules in studying the effect of granule properties on the pore structure of tablets.

Gold et al. (1971) described the use of an apparatus consisting of a motor-driven cam with a cantilever beam and strain gauges to determine the granule strength. A compressive load proportional to a millivolt

response was applied to the granule which was measured on a recorder.

Ganderton and Hunter (1971) measured granule strength by determining resistance to fracture. This involved using a miniature press with a moving lower platen and a fixed upper platen to which a load cell was attached. They discussed the effect of preparing granules by pan granulation and by massing and screening which included a study of the effect of processing variables on the work done in crushing such particles.

Erni and Ritschel (1977) describe a piece of apparatus based on a vertical, modified disposable syringe. Preliminary work involved determining the pressure resistance of granules by the addition of weights into the plunger part of the syringe container. Pressure resistance was measured by using a load less than that determined necessary by the pre-test to crush the particle, to which water is added from a burette into the syringe until fracture occurred. The load required to crush the granule was then calculated from the sum of the weights and the volume of water added to the system.

Ahuja (1977) studied the critical stresses of brittle and ductile polymeric spheres. This author describes a single-particle crush apparatus utilising strain gauges. The strain indicator sends a signal on deflection of a metallic strip, which is expressed as an amplified voltage and fed to a chart recorder. A glass probe was inserted through the metallic strip which was sensitive to vertical and horizontal displacement. Even for chemically homogeneous small spheres it was anticipated that there would be a distribution of particle strengths as a result of the inherent morphological characteristics, micro-cracks or small voids.

Krogh (1980) discussed a method based on drop weights as a technique for crushing particles. This author illustrated that particles of the same size do not possess the same tensile strength.

Kuno and Okada (1982) studied the compaction process and the deformability of granules. They summarised their work by claiming that crushing a particle is composed of two sequential stages; the first stage involving rearrangement and deformation of particles and second to this, the crushing stage. Properties of the granules including the porosity and elasticity, affect that stress which must be applied to cause particle fracture. These authors describe apparatus for measuring strength and deformability of single granules. Load is applied to the granule by pouring water from a reservoir into a bucket hanging on a lever. Stress applied to the granule was detected by a transducer on which the granule was placed. A transformer detected any displacement of the diameter of the particle which was expressed as linear shrinkage by these authors.

Jarosz and Parrott (1983) described a method for measuring the crushing strength of granules. This technique involved the use of glass syringes which were modified to act as a load cell to which mercury was added from a reservoir until the granule was crushed.

Tanaka et al. (1985) described equipment used in the determination of crushing strength of ferrite particles. A Rockwell Hardness Tester was employed. Load was applied to the particles manually and the crush load monitored by a load cell underneath the lower anvil. The crushing force was read from a recorder from which crushing stresses were calculated. Results were expressed graphically as crushing stress (MPa) against particle size (micrometers). A great degree of scatter was evident. This scatter was explained as being attributive to crack initiation occurring in the vicinity of that part of the particle in contact with one of the anvils. The implication being that plastic surface penetration at the contact surface is the cause of the crack initiation. The authors in fact confirmed that the crushing stress of ferrite is related to the fundamental hardness of the material and is

independent of particle size.

Wan and Jeyabalan (1986) described the use of a simple technique to measure the crushing strength of spherical granules involving water flowing slowly from a reservoir into a plastic container placed on a pellet. The weight of water required to cause pellet fracture was interpreted as the crushing strength of that particle.

The aim of this present study involving the a determination of the crushing characteristics of both placebo and active pellets containing a high ibuprofen content was to acquire an insight into the physical strength and elasticity of such formulations. This information was required in order that a suitable pellet formulation may be designed, such that the integrity of the pellet cores and that of an applied film coating may be maintained even during compression of pellets with an inert diluent blend into tablets.

The mechanical strength of a pellet is related to the nature of the excipients from which it is composed, the cross-sectional area, the quality of the geometry of the sphere and inherent physical parameters determined by the manufacturing process; these include massing, extrusion and spheronisation variables and the drying method employed. These parameters all contribute to the elastic, plastic and fragmentary properties of the pellets. Pellet porosity and density are also affected by these variables associated with the manufacturing technique.

6.2. Methods.

6.2.1. Single Particle Crushing Assembly.

Determination of the tensile properties of pellets, active and placebo, uncoated and coated, was facilitated by determining the force required to cause pellet fracture using the Single Particle Crushing Assembly. The use of this technique yielded quantitative information relating to the crushing strength, pellet displacement under applied

stress, percentage strain and the elastic modulus of pellets. These parameters were sought in order to study those formulation factors influencing the tensile properties of uncoated pellets, the manufacturing technique and the effect of film coating of pellets on the resultant mechanical properties.

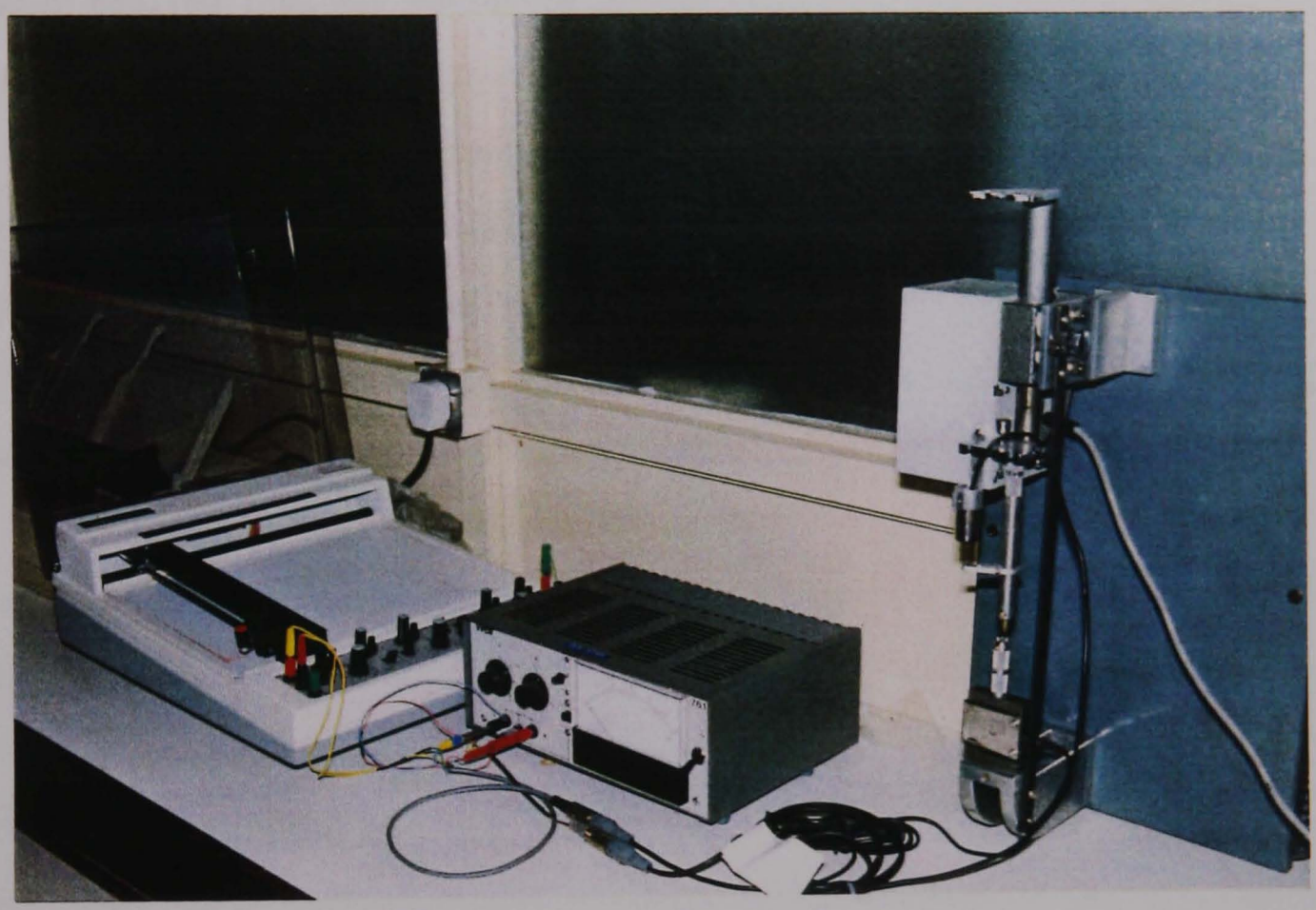


Figure 6.4. Photographic illustration of the Single Particle Crushing Assembly.

The Single Particle Crushing Assembly (Figure 6.4) consisted of a highly sensitive load cell (U-4000, Maywood Instruments Ltd. Basingstoke) which was sensitive to a maximum load of 50N and capable of a high dynamic response as a result of a low deflection under load. This particular load cell used transducer strain gauges in a full bridge configuration bonded to a transduction element. A motorised unit to which an upper brass pointer was connected, was set to approach the

pellet mounted on a lower platen at a given rate. The load applied to the pellet was detected by the strain gauges, converted into a millivolt response and recorded on a calibrated X-Y chart recorder. An excitation energy of 10 volts was maintained throughout. Figure 6.5 is a schematic representation of the Single Particle Crushing Assembly.

The chart recorder was calibrated so that displacement of the pellet under applied load was reflected on the x-axis; a 1mm diameter pellet displacement being equivalent to 100mm on the chart recorder.

Similarly the load applied to each pellet was recorded on the y-axis; a force of 5N was represented by a distance of 100mm on the chart recorder. Pellet diametral measurements were made in the X and the Y plane using a digital micrometer (Mitustoyo, Japan); the mean diameter of each randomly selected pellet was therefore determined.

Determination of pellet dimensions together with quantitative information in respect of the applied load and as a consequence particle displacement, enabled calculation of pellet cross-sectional area, applied stress and strain, work done in causing particle fracture and the relative elasticity of those formulations under test.

That force causing pellet fracture is represented on the X-Y chart recording by a maximum peak just prior to fracture. For a pellet fracturing into many progeny units, the break will manifest itself as a sharp peak on the chart. For a pellet showing very little fragmentation after crushing, resulting in a fewer, larger particles, the peak representing the fracture may not necessarily be the highest point on the chart, since further application of force to the fractured material will result in further fragmentation of the progeny particles.

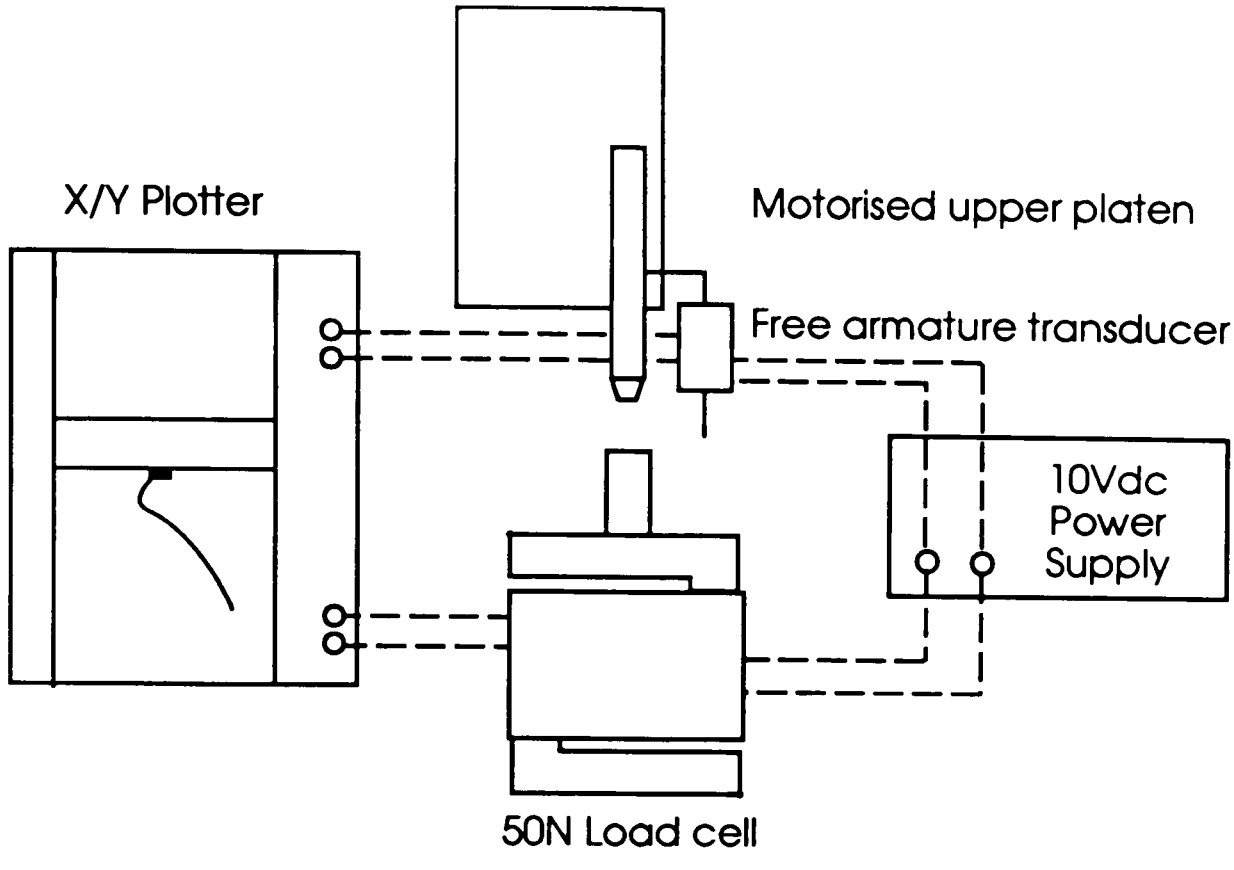


Figure 6.5. Schematic illustration of the Single Particle Crushing Assembly.

6.2.2. Determination of the tensile properties of pellets as a consequence of fracture under applied load.

On application of a force (F) to a particle of diameter (D), the particle will exhibit a degree of deformation or displacement (d), in the direction of that force. The work done (Nm) in causing particle fracture may therefore be defined as the product of that force (N) causing fracture and displacement (m) in the direction of the applied force (Equation 6.1):

work done = force x displacement Equation 6.1.

With this technique force is being applied to a spherical particle and

therefore the work done in causing pellet fracture is represented by the area under the force-displacement peak on the X-Y chart recording.

The force per unit area (F/A) producing the deformation of a solid particle is termed the tensile stress (σ). For a spherical particle or pellet therefore, tensile stress may be defined as follows:

$$\text{stress} = \frac{\text{force}}{\text{maximum cross-sectional area}} = \frac{4F}{\pi D^2} \qquad \text{Equation 6.2.}$$

The elastic deformation exhibited by a particle on the application of load is termed the strain, which may therefore be defined as the relative change in dimension in the direction of the force.

The linear tensile strain (or relative elongation or displacement) ϵ, exhibited by a sphere on the application of load is therefore defined as the change in diameter (or pellet displacement) in the direction of the applied force (Equation 6.3).

$$\text{strain } \epsilon = \frac{\text{displacement}}{\text{diameter}} \qquad \text{Equation 6.3.}$$

The units of displacement and diameter are both units of length and strain is thus a dimensionless parameter.

The elastic modulus of a material may be defined as the ratio of tensile stress to linear strain, since for elastic material there is a linear relationship between these two parameters

$$\sigma = E\,\epsilon \qquad \text{Equation 6.4.}$$

where E is the elastic modulus.

Substituting Equation 6.2 into Equation 6.4 therefore

$$\frac{F}{A} = \frac{4F}{\pi D^2} = E\frac{d}{D} \qquad \text{Equation 6.5.}$$

where d is the displacement exhibited by a pellet of diameter D, on the application of force. E is the proportionality constant or the elastic modulus of the material.

6.2.3. Composition of pellet formulations studied.

Precise formulation and manufacturing details for those pellet formulations studied are given in Chapter 3.

Briefly, uncoated pellets were manufactured using the technique of extrusion-spheronisation using either bench or pilot scale massing and spheronisation equipment, and an Alexanderwerk GA65 Extruder. Pellets were dried using Aeromatic fluidised bed apparatus (of 1L or 10L capacity), or by tray drying in a hot air oven. The film coating of ibuprofen pellets using aqueous polymeric dispersions of different polymers is discussed previously in Chapter 3. Pellets were film coated using a 1L Aeromatic fluidised bed apparatus with a stainless steel chamber and top spray attachment.

A study of the tensile properties of placebo and ibuprofen-containing pellets in respect of formulation factors, scale of the manufacturing equipment used, drying technique and the presence or otherwise of a film coat, was facilitated using the Single Particle Crushing Assembly described in this work. In addition to obvious reasons for studying the aforementioned variable parameters, determination of the tensile properties of pellets was necessary within the scope of this work involving a presentation of a monolithic drug delivery device composed of polymer coated multiparticulates, in order to ascertain the relative

mechanical properties of these units. Identification of those pellet and film coating formulations able to withstand the compression process was necessary in order to at least minimise or at best prevent, an impairment of the integrity of both the polymeric membrane and the pellet core as a consequence of compression into tablets.

6.3. Results and Discussion.

The resistance of individual particles to crushing is related to the excipients from which they are composed, their geometric size and shape, and any physical parameters incorporated as a result of the manufacturing process.

The physical properties of pellets are influenced by many factors including the volume of the granulating fluid; variables associated with the mixing/massing processing procedure; the size of the holes of the perforated screen and the rate of extrusion of granulate; the spheronisation plate weight, residence time and rotation speed; the drying technique and therefore the length of the drying process. Whichever combination of these parameters exists for any given pellet formulation, there will be an influence on the matrix structure and the elastic, plastic and fragmentary properties of the resultant product.

6.3.1. Effect of drug loading on the tensile properties of uncoated pellets dried using fluidised bed apparatus.

Table 6.1 summarises the mechanical properties of uncoated pellets containing ibuprofen which were dried using fluidised bed apparatus. These parameters were calculated using the data obtained from the force-displacement curves, as described in section 6.2.2. A mean of approximately forty pellets were evaluated using this quantitative fracture test. Graphical evaluation of the data indicated that there appeared to be a direct linear relationship between pellet crushing force

and diameter; work done in causing pellet fracture and displacement on the application of stress; % strain and pellet displacement; crushing force and work done and work done and % strain. There was however a substantial degree of scatter in these plots (Appendix II). The quality of the spheres, defects in surface characteristics including irregularity of shape or penetrative cracks in pellets, the internal pore structure and the skeletal density of pellets are all factors which may realistically have contributed to this scatter. It was considered that the information provided by such graphical interpretations was of limited value in isolation and that tensile properties could better be expressed either tabulated or in the form of a comparative illustration (as a histogram) for a range of related pellet formulations. Using the available pellet particle size range therefore (determined largely by the screen size of the perforated cylinder of the extruder), mean values were determined for the force required to cause pellet fracture, pellet displacement, work done, % strain, stress and the elastic modulus for pellets of mean particle size. This form of data manipulation enables comparative evaluation of the tensile properties of pellets as a consequence of formulation factors and processing variables.

Table 6.1 clearly shows the effect of drug loading and the corresponding microcrystalline cellulose (Avicel PH101) content of uncoated pellets containing ibuprofen on the tensile properties of pellets dried using fluidised bed apparatus. A decrease in the drug content with a corresponding increase in the quantity of microcrystalline cellulose content of uncoated ibuprofen pellets results in pellets of greater mechanical strength (Figure 6.6) exhibiting greater displacement, % strain and stress and for which more work is required to cause pellet fracture. Figure 6.7 shows that with decreasing Avicel content there is a corresponding increase in the elastic modulus representing a decrease in the pellet elasticity. The presence of increased microcrystalline

cellulose content in pellet formulations has the effect of enhancing the cohesion between the components of the blend, therefore those pellets containing only 20%w/w Avicel PH101 are less robust and more elastic than those containing 40%w/w Avicel PH101.

In summary, pellets containing a high ibuprofen content exhibit the greatest elasticity although the force required to cause pellet fracture is less than for those containing the higher microcrystalline cellulose content.

The significance of the drying technique used in the preparation of pellets containing ibuprofen (poorly water soluble) and in placebo pellet manufacture, with a highly water soluble component (lactose) is discussed in section 6.3.2.

	%w/w ibuprofen		
	80	70	60
bead diameter (μm)	1107 *935-1230	1091 976-1212	1125 979-1249
crushing force (N)	2.59 1.30-3.28	3.45 2.03-4.88	4.91 3.00-7.13
displacement (μm)	86 55-145	89 60-125	92 45-120
work done (μJ)	113 36-202	155 75-233	229 74-428
% strain	7.79 4.58-12.7	8.16 5.5-11.89	8.17 4.09-10.34
stress(MPa)	2.72 1.15-3.88	3.71 2.28-5.25	4.94 2.94-6.36
n	47	46	48

NB: all values represent the mean of n samples
* = range values

Table 6.1. Effect of drug loading on the mechanical properties of uncoated pellets containing ibuprofen.

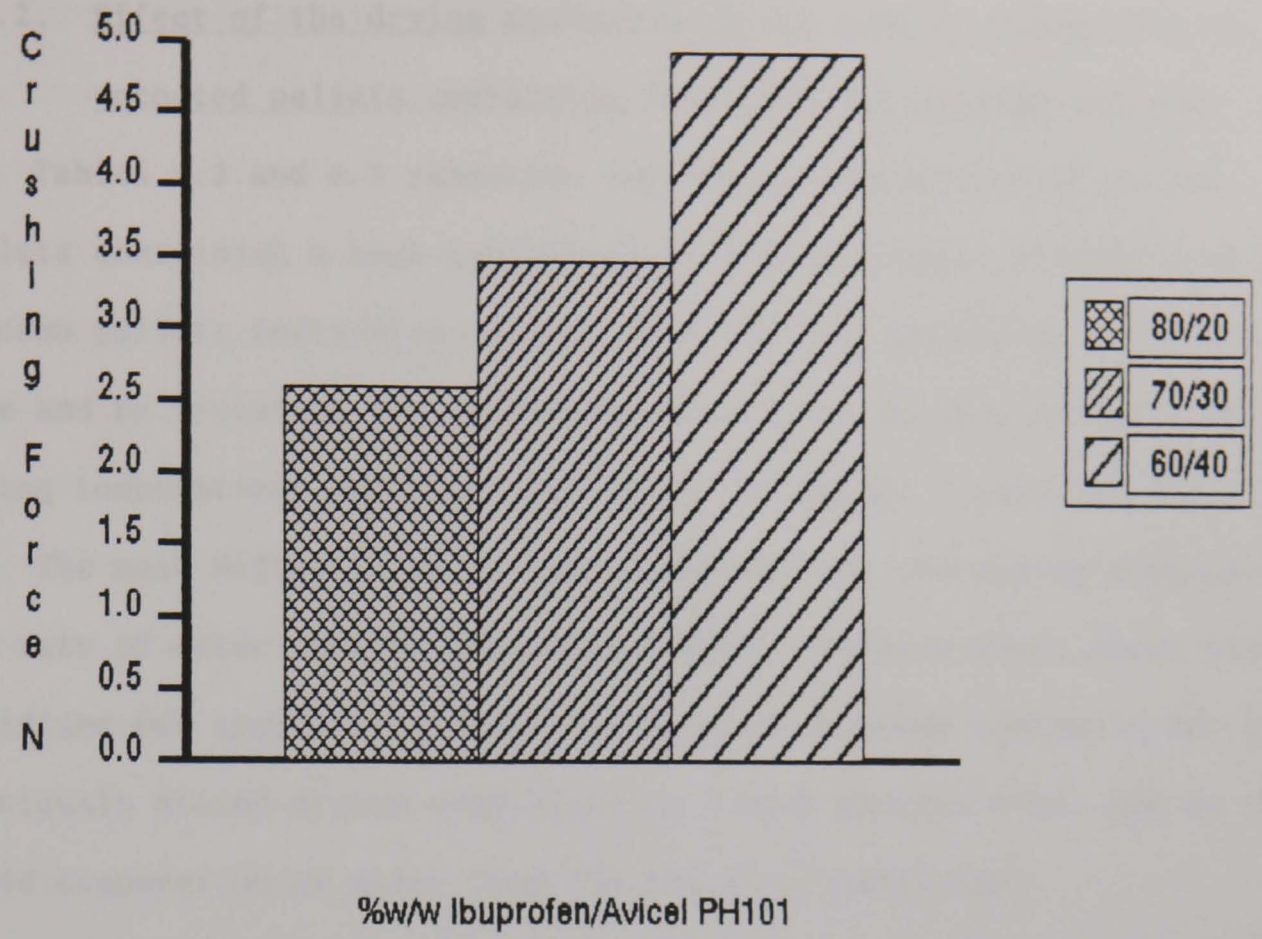


Figure 6.6. Effect of drug loading on the mechanical strength of ibuprofen pellets dried using fluidised bed apparatus.

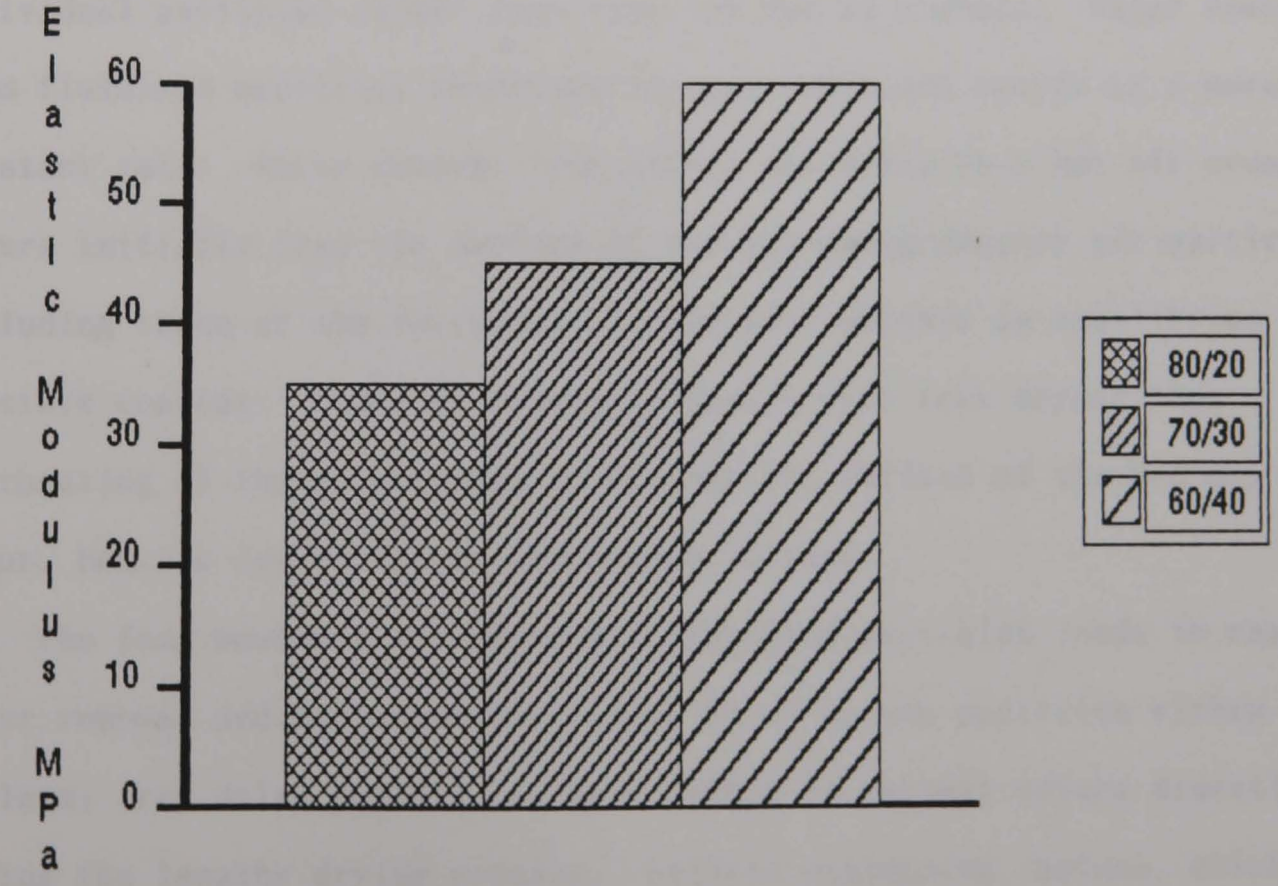


Figure 6.7. Effect of drug loading on the elastic modulus (MPa) of ibuprofen pellets dried using fluidised bed apparatus.

6.3.2. Effect of the drying technique on the tensile properties of uncoated pellets containing ibuprofen and placebo pellets.

Tables 6.2 and 6.3 summarise the tensile properties of active pellets containing a high percentage of a poorly water soluble drug and placebo pellets containing lactose dried by tray drying in a hot air oven and by fluidised bed methodology. Precise details relating to the drying temperatures and times are given in Chapter 2 (section 2.2).

The main differentiating factor between the two drying methods is the rate of water removal from the pellets. Those pellets dried using fluidised bed apparatus achieve the desired moisture content under the previously stated drying conditions in a much shorter time, due to the rapid evaporation of water from the fluidised particles.

Water removal from tray dried material is slow by virtue of the fact that poor heat and mass transfer is associated with material which is static. The fluidised state of the bed enables water removal from individual particles rather than from the bed as a whole. Water removal from fluidised particles therefore is more rapid and occurs at a more constant rate. Water removal from static particles in a hot air oven occurs initially from the surface of the bed and gradually all particles including those at the bottom of the bed will achieve an equilibrium moisture content. There is however a danger with tray drying that overheating of those particles at or near the surface of the bed may occur, hence a lower drying temperature is used.

The free movement of individual fluidised particles leads to rapid water removal and minimises the migration of solute particles within the pellets; tray dried pellets are more likely to exhibit solute migration during the lengthy drying process. Pellets containing lactose, which is freely soluble in the granulating fluid, are highly susceptible to the process of solute migration as a consequence of the drying times associated with static bed dryers.

During the drying process any residual moisture in the product leads to the formation of solid bridges in the granules by fusion at the point of contact. For solute particles (for example lactose, dissolved in the granulating fluid), crystallisation of the dissolved particles will cause a greater of bonding and hence a mechanically stronger particle. Placebo pellets therefore are mechanically stronger than drug-containing entities (c.f. Figures 6.8 and 6.10). The drying method also has an effect on the elastic modulus of both ibuprofen-containing pellets and placebo pellets (Figures 6.9 and 6.11). Ibuprofen is virtually insoluble in water and it is reasonable to expect little re-crystallisation of solute particles during the drying process. Conversely lactose is freely soluble; lactose-containing pellets exhibit a high degree of solute migration and crystallisation during the drying process. This leads to mechanically stronger, less elastic, brittle particles (Figures 6.8 to 6.11).

Slower water removal from ibuprofen-containing pellets by tray drying rather than fluidised bed drying, leads to limited solute migration as a consequence of the aqueous solubility of this drug. This is supported by the relative drug release rates as indicated by the *in-vitro* dissolution profiles (Figure 2.17). Drug release from tray dried pellets is slightly enhanced when compared with that from fluidised bed dried particles.

In summary, the drying technique for a given uncoated pellet formulation has a significant effect on the tensile properties of pellets prepared by extrusion-spheronisation methodology. Pellets dried by tray drying require a greater crushing force and the work done in causing pellet fracture is therefore greater. Tray dried entities also exhibit greater displacement prior to fracture and are able to withstand greater strain and stress than the fluidised bed dried entities. Fluidised bed dried pellets however demonstrate greater elasticity; this is reflected in the relatively low elastic modulus values obtained.

The solubility of the excipients from which pellets are composed affects the degree of solute migration occurring during the drying process. The drying method, and as a consequence the length of the drying process, also affects the degree of solute migration and is highlighted by the *in-vitro* release profile for ibuprofen pellets dried using these two methodologies.

	Drying Method	
	tray	fluidised bed
bead diameter (μm)	1093 *881-1269	1086 878-1343
crushing force (N)	2.81 0.9-4.25	1.91 1.0-3.05
displacement (μm)	88 65-170	67 40-110
work done (μJ)	127 32-298	67 23-167
% strain	8.1 6.3-15.1	6.2 4.0-8.9
stress(MPa)	3.0 1.48-4.31	2.06 1.14-3.51
n	48	44

NB: all values represent the mean of n samples
* = range values

Table 6.2. Effect of uncoated pellet drying method on the mechanical properties of uncoated pellets containing 80%w/w ibuprofen.

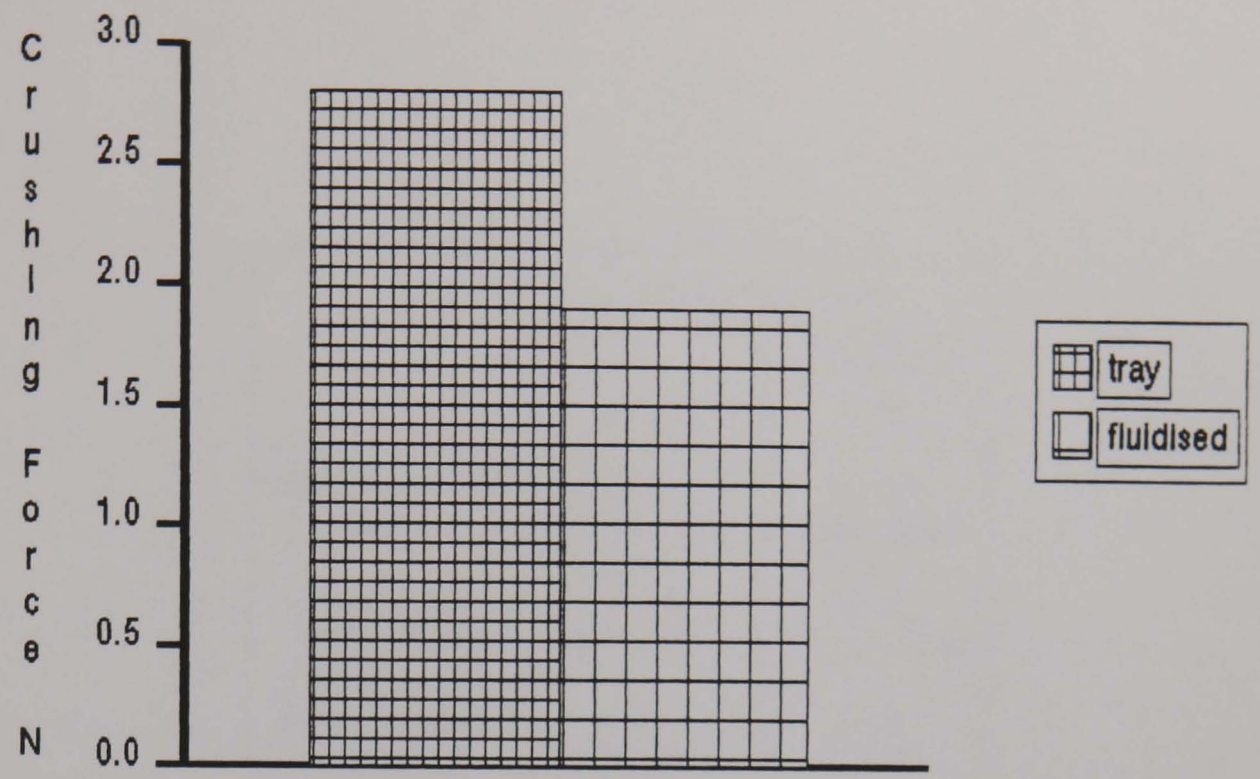


Figure 6.8. Effect of the drying technique on the mechanical strength of uncoated pellets containing 80%w/w ibuprofen.

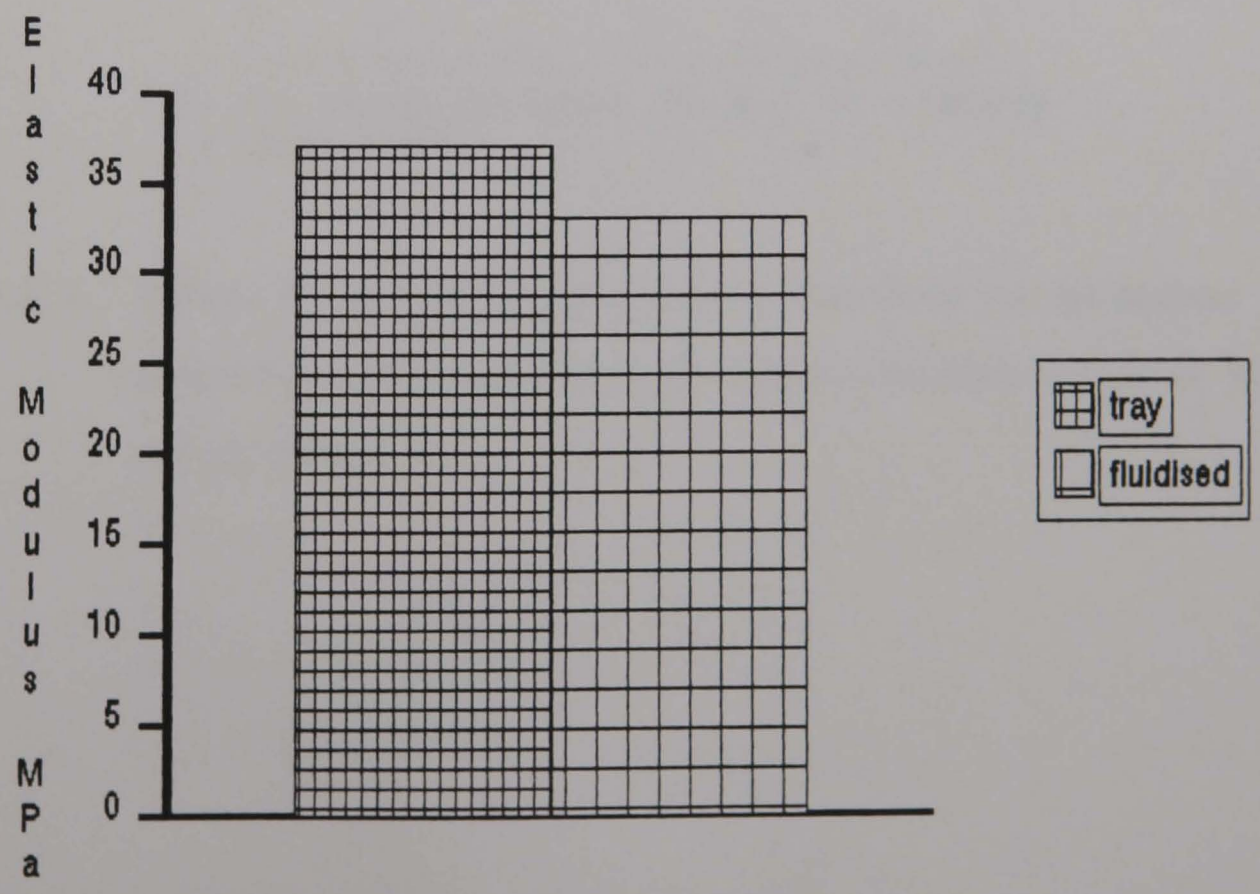


Figure 6.9. Effect of the drying technique on the elastic modulus (MPa) of uncoated pellets containing 80%w/w ibuprofen.

	Drying Method	
	tray	fluidised bed
bead diameter (μm)	1073 *915-1235	1080 909-1201
crushing force (N)	14.0 8.8-18.3	9.0 5.1-12.8
displacement (μm)	168 110-270	122 75-210
work done (μJ)	1197 539-2333	535 191-903
% strain	15.7 10.3-24.1	11.4 6.6-21.5
stress(MPa)	15.5 10.8-23.2	9.4 5.9-13.1
n	40	44

NB: all values represent the mean of n samples
* = range values

Table 6.3. Effect of uncoated pellet drying method on the mechanical properties of placebo pellets containing 80%w/w lactose with Avicel PH101.

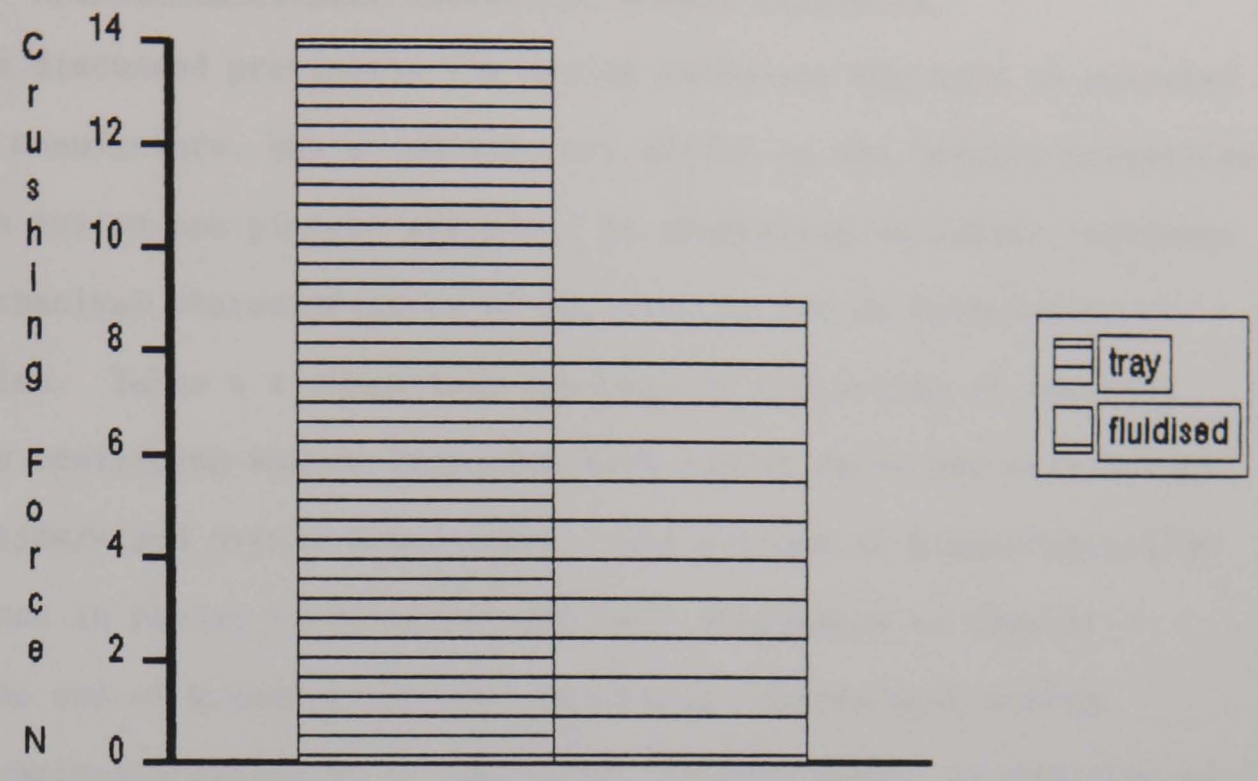


Figure 6.10. Effect of the drying technique on the mechanical strength of placebo pellets containing 80%w/w lactose with Avicel PH101.

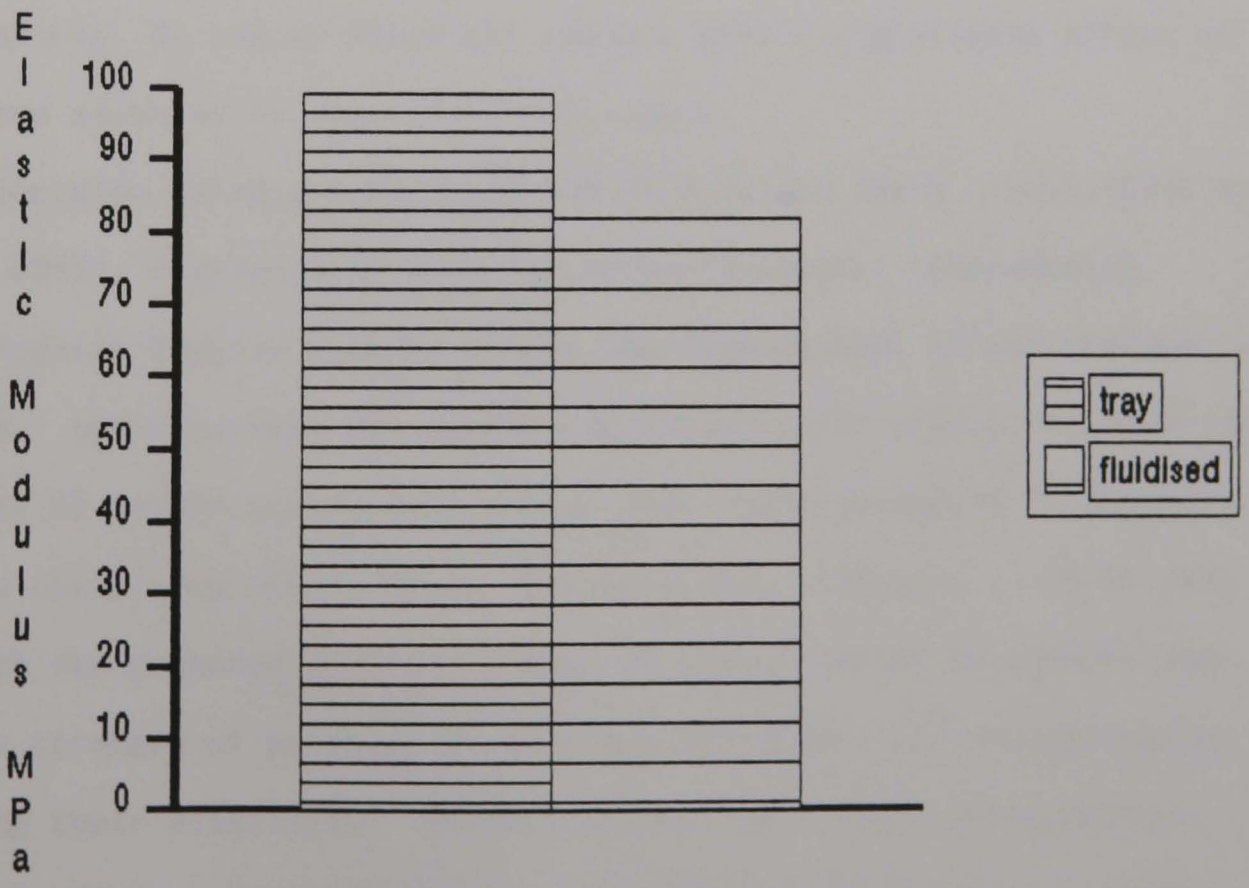


Figure 6.11. Effect of the drying technique on the elastic modulus (MPa) of placebo pellets containing 80%w/w lactose with Avicel PH101.

6.3.3. Effect of the uncoated formulation on the tensile properties of tray dried pellets containing 80%w/w ibuprofen.

As discussed previously the drying technique employed in uncoated pellet manufacture, has a contributory effect on the tensile properties of both active and placebo pellets. As processing variables influence the mechanical characteristics of pellets, so too do formulation variables. Table 6.4 summarises the tensile properties of uncoated pellets containing 80%w/w ibuprofen with Avicel PH101 and with Avicel PH101 15%w/w and Avicel CL611 5%w/w. The virtues of microcrystalline cellulose in pellet formulations are well documented in Chapter 2.

The use of grades of Avicel containing incorporated sodium carboxymethylcellulose as an additional binding agent, in addition to facilitating the preparation of pellets containing an even higher drug content than is possible with Avicel PH101 alone, facilitate the preparation of ibuprofen pellets with a greater mechanical strength. It is evident that even very low percentages of Avicel CL611 in pellet formulations, as low as 5%w/w for example have a significant effect on the force required to cause pellet fracture.

Ibuprofen pellets containing 80%w/w drug and 5%w/w Avicel CL611 with Avicel PH101, require more work for pellet fracture; they exhibit significantly greater strain, stress and displacement on the application of load. Those pellets not containing Avicel CL611 require a force for fracture of approximately only 56% of that force necessary to fracture pellets containing Avicel CL611 (Figure 6.12). Figure 6.13 shows that although the presence of CL611 grades of Avicel serves to enhance the tensile strength of pellets, it also has the effect of simultaneously reducing their elasticity. Pellets containing sodium carboxymethyl-cellulose grades of Avicel therefore exhibit a higher elastic modulus than those which do not. A similar effect was observed for those pellet formulations containing Avicel RC591NF.

	Pellet Composition	
	20%w/w Avicel PH101	15:5 Avicel PH101:CL611
bead diameter (μm)	1093 *881-1269	993 725-1220
crushing force (N)	2.81 0.9-4.25	5.0 2.7-7.7
displacement (μm)	88 65-170	141 50-280
work done (μJ)	127 32-298	352 74-918
% strain	8.1 6.3-15.1	14.0 6.3-32.5
stress(MPa)	3.0 1.48-4.31	6.0 3.51- 9.13
n	48	39

NB: all values represent the mean of n samples
* = range values

Table 6.4. Effect of uncoated pellet formulation on the mechanical properties of tray dried pellets containing 80%w/w ibuprofen.

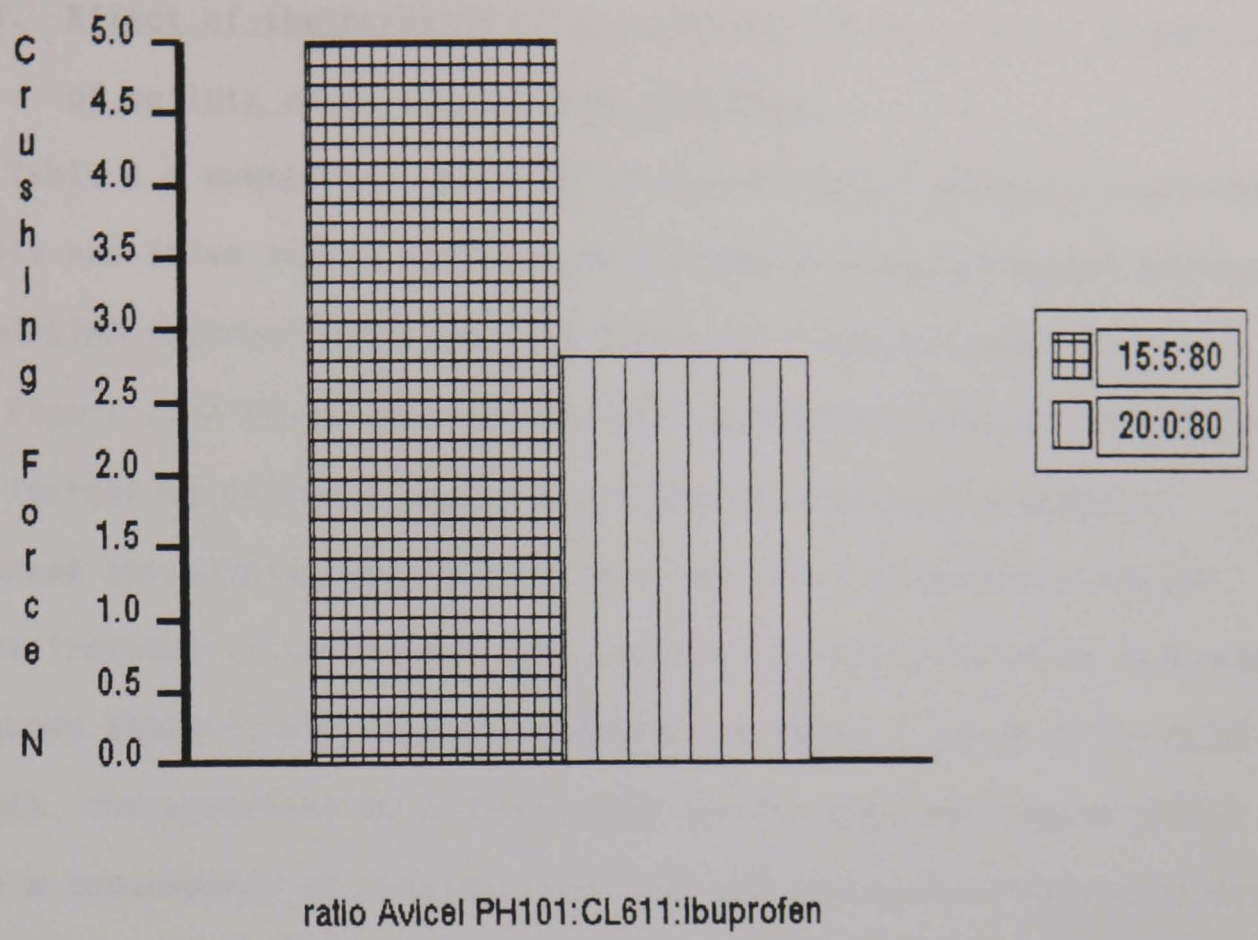


Figure 6.12. Effect of the inert excipients on the mechanical strength of tray dried pellets containing 80%w/w ibuprofen.

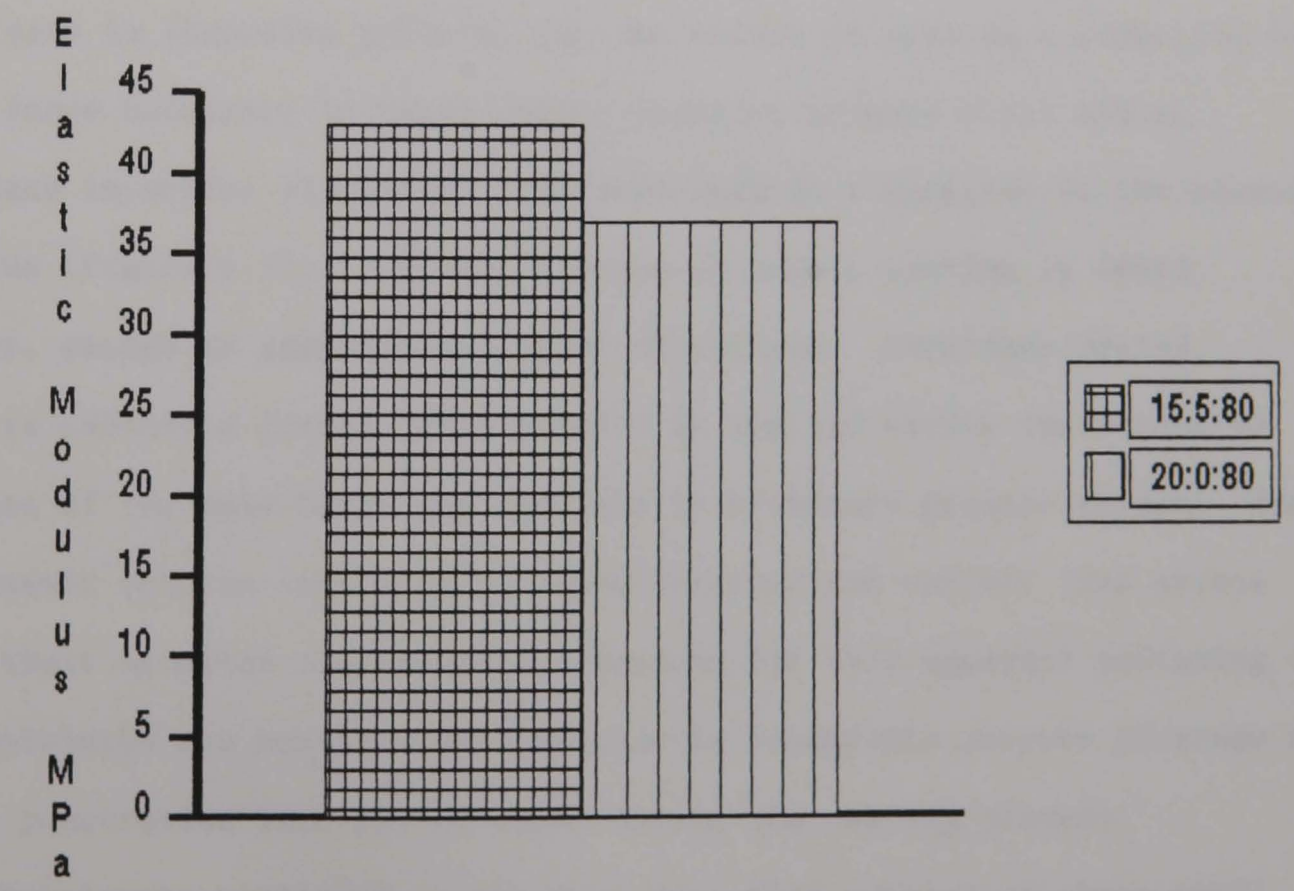


Figure 6.13. Effect of the inert excipients on the elastic modulus (MPa) of tray dried pellets containing 80%w/w ibuprofen.

6.3.4. Effect of the presence of a film coat on the tensile properties of pellets containing 80%w/w ibuprofen.

Table 6.5 summarises the tensile properties of uncoated ibuprofen pellets and those coated with aqueous polymeric dispersions of Eudragit RS30D/RL30D (polymethacrylate) and Surelease (ethylcellulose).

Figure 6.14 shows that for pellets coated with Eudragit RS30D/RL30D, with increasing polymer loading and therefore increasing membrane thickness surrounding the pellet core, the force necessary to cause pellet fracture is correspondingly increased. With increased membrane thickness there is also a corresponding increase in the elasticity of the pellets, characterised by a decreasing elastic modulus (Figure 6.15). Hence a consequence of coating ibuprofen pellets with a release retarding membrane of the polymethacrylates, is enhanced pellet elasticity and increased pellet tensile strength.

Conversely however, the application of a polymeric membrane of Surelease to ibuprofen pellets, has the effect of causing a reduction in that force necessary to cause pellet fracture (Figure 6.16) and an increase in pellet elasticity, characterised by a decrease in the elastic modulus (Figure 6.17). The application of such a coating it would appear, causes an apparent softening of pellets. Surelease coated pellets exhibit a greater displacement on applied stress than uncoated pellets of the same batch and are able to withstand greater strain. They do however require less work to cause fracture and exhibit less stress than their uncoated counterparts. Reasons for this apparent softening it is postulated are possibly attributable to incomplete polymer coverage or water penetration into pellet cores during the coating process.

Previously mentioned is the fact that film coating of these small multiparticulates using fluidised bed apparatus is not without problems. The ethylcellulose formulation exhibits a tendency to form a tacky film under the operating conditions of the film coating chamber and careful

temperature monitoring is required throughout in order that pellet agglomeration is prevented during coating. Furthermore the manufacturers claim and this work has confirmed, that an overcoat formulation of Opadry is necessary to prevent pellet agglomeration following application of the ethylcellulose film. Pellets not coated with the overcoat formulation display sticking tendencies even under ambient conditions. It is feasible that a certain degree of water penetration into the pellet cores occurs during the initial stages of the coating process a consequence of which is pellet softening. The conferred enhanced elasticity of pellets coated with Surelease is not unexpected due to the exceedingly high instantaneous and time-dependent elasticities and low elastic modulus and Newtonian viscosity exhibited by free-films of this polymeric formulation (Chapter 5).

6.3.5. Assessment of the mechanism of pellet fracture on applied stress.

Figures 6.18 and 6.19 show photographs of pellet fracture both prior to and after the application of stress. Many photographs were taken during pellet fracture; negligible differences were noticeable under these test conditions. It has been shown that the presence of a film coat surrounding a pellet core serves to enhance the elasticity of such a pellet as characterised by the elastic modulus. However, no visibly detectable differences were observed in the mechanism of pellet fracture during the crushing of these multiparticulates.

Initially on load application and within the elastic limit of the particle, stress is directly proportional to strain. As the elastic limit of the particle is exceeded however, permanent deformation is followed by particle fracture. The occurrence of permanent deformation of a solid results in energy expansion and the formation of cracks; the furthest extension of a crack is the area of greatest stress.

	Coating Status			
	Uncoated	Eudragit 4.5%w/w increase	Eudragit 12%w/w increase	Surelease 10%w/w increase
bead diameter (μm)	1107 *935-1230	1145 1044-1272	1144 988-1254	1132 959-1248
crushing force (N)	2.59 1.30-3.28	2.74 1.53-3.78	2.81 1.65-3.75	2.13 0.78-3.65
displacement (μm)	86 55-145	89 50-250	94 65-140	103 55-200
work done (μJ)	113 36-202	126 47-473	133 54-218	108 41-230
% strain	7.79 4.58-12.7	7.81 4.27-23.95	8.25 5.8-14.17	9.05 5.23-15.61
stress(MPa)	2.72 1.15-3.88	2.66 1.53-4.42	2.74 1.67-4.16	2.13 0.78-3.25
n	47	46	51	43

NB: all values represent the mean of n samples
* = range values

Table 6.5. Effect of the presence of a film coat on the mechanical properties of pellets containing 80%w/w ibuprofen.

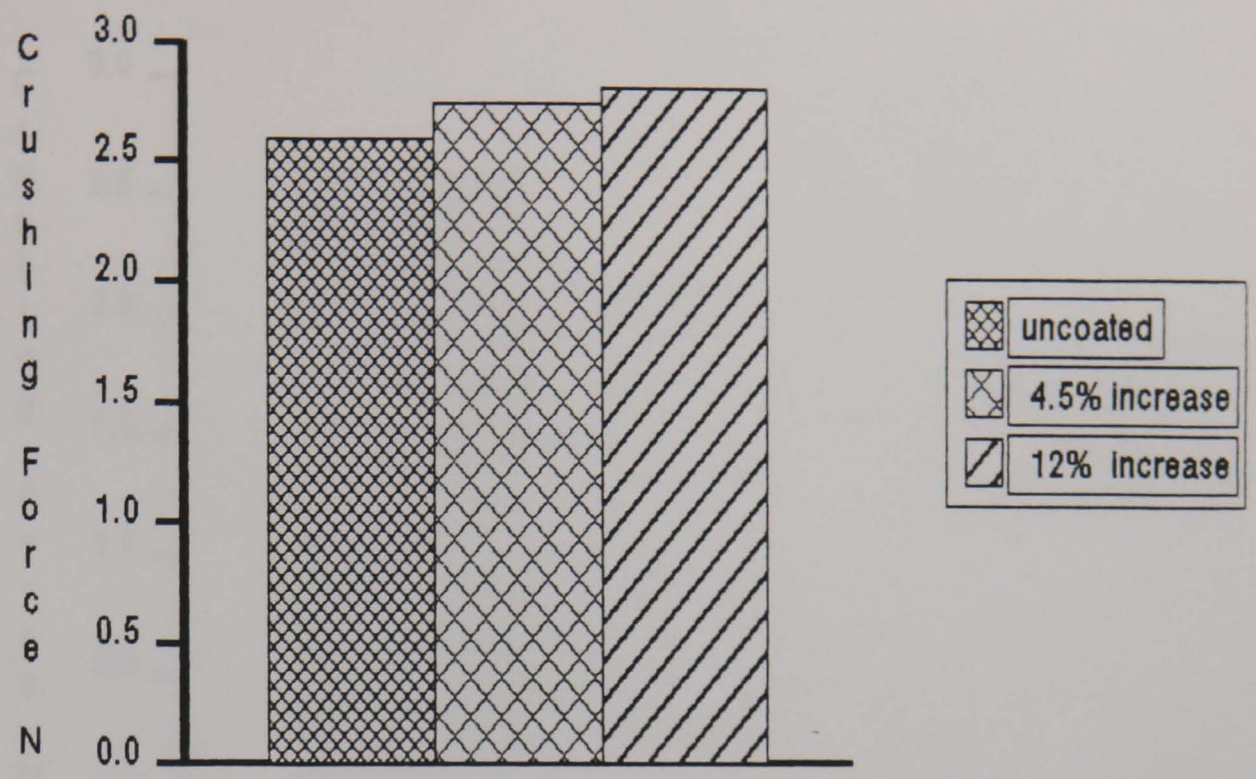


Figure 6.14. Effect of a film coat of Eudragit RS/RL30D on the mechanical strength of fluidised bed dried pellets containing 80%w/w ibuprofen.

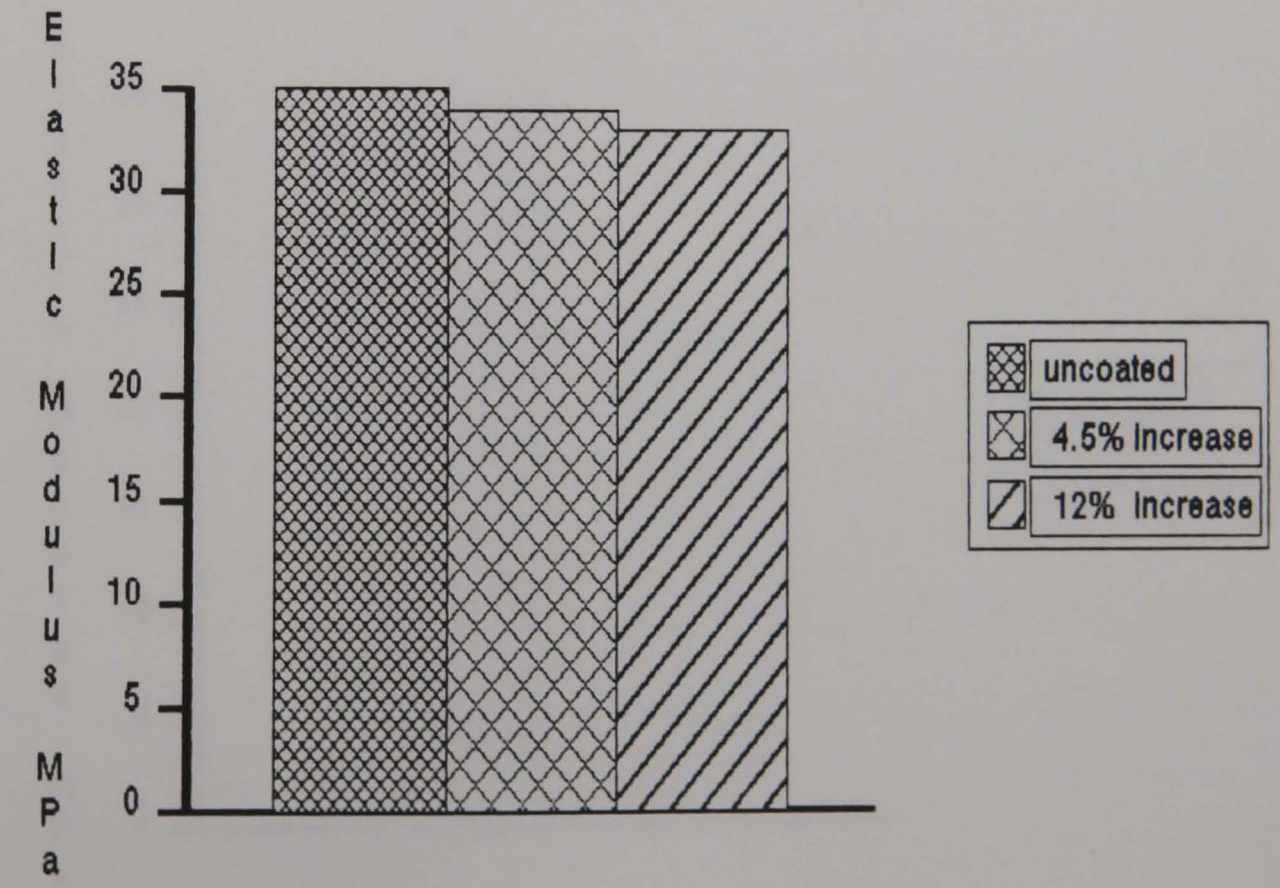


Figure 6.15. Effect of a film coat of Eudragit RS/RL30D on the elastic modulus (MPa) of fluidised bed dried pellets containing 80%w/w ibuprofen.

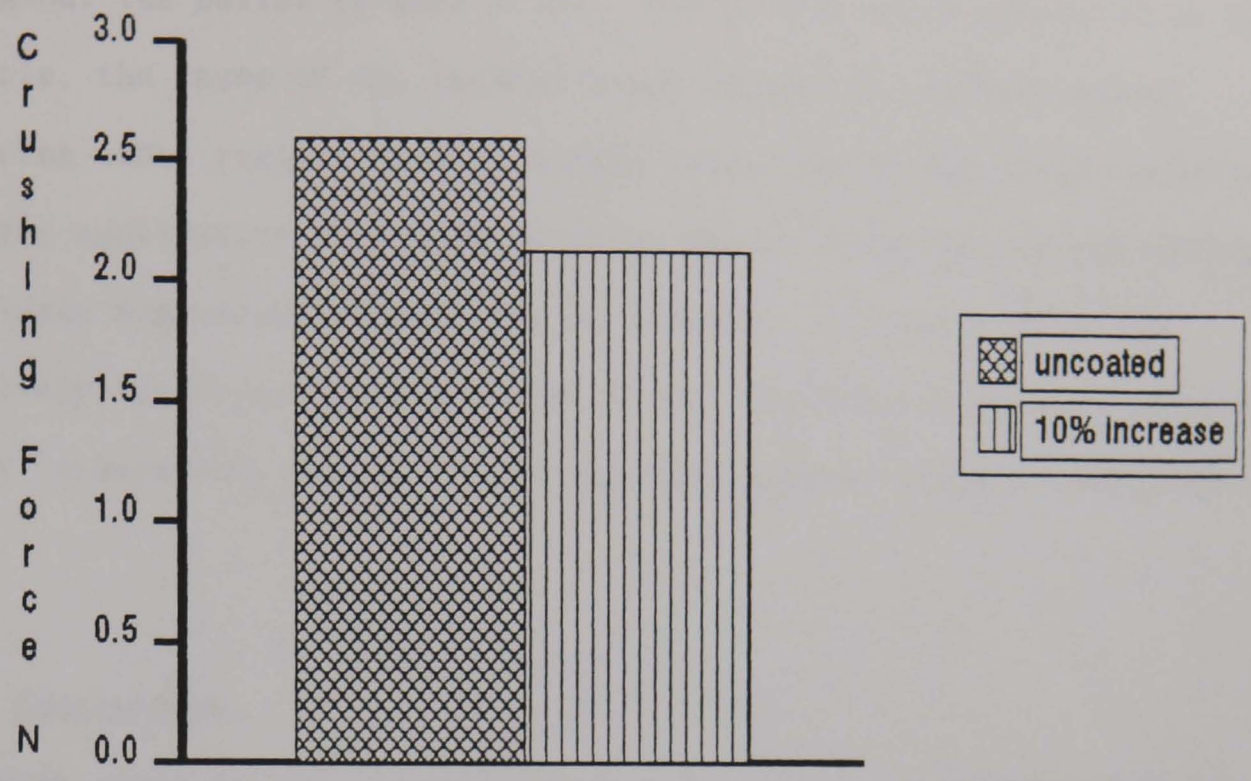


Figure 6.16. Effect of a film coat of Surelease (ethylcellulose) on the mechanical strength of fluidised bed dried pellets containing 80%w/w ibuprofen.

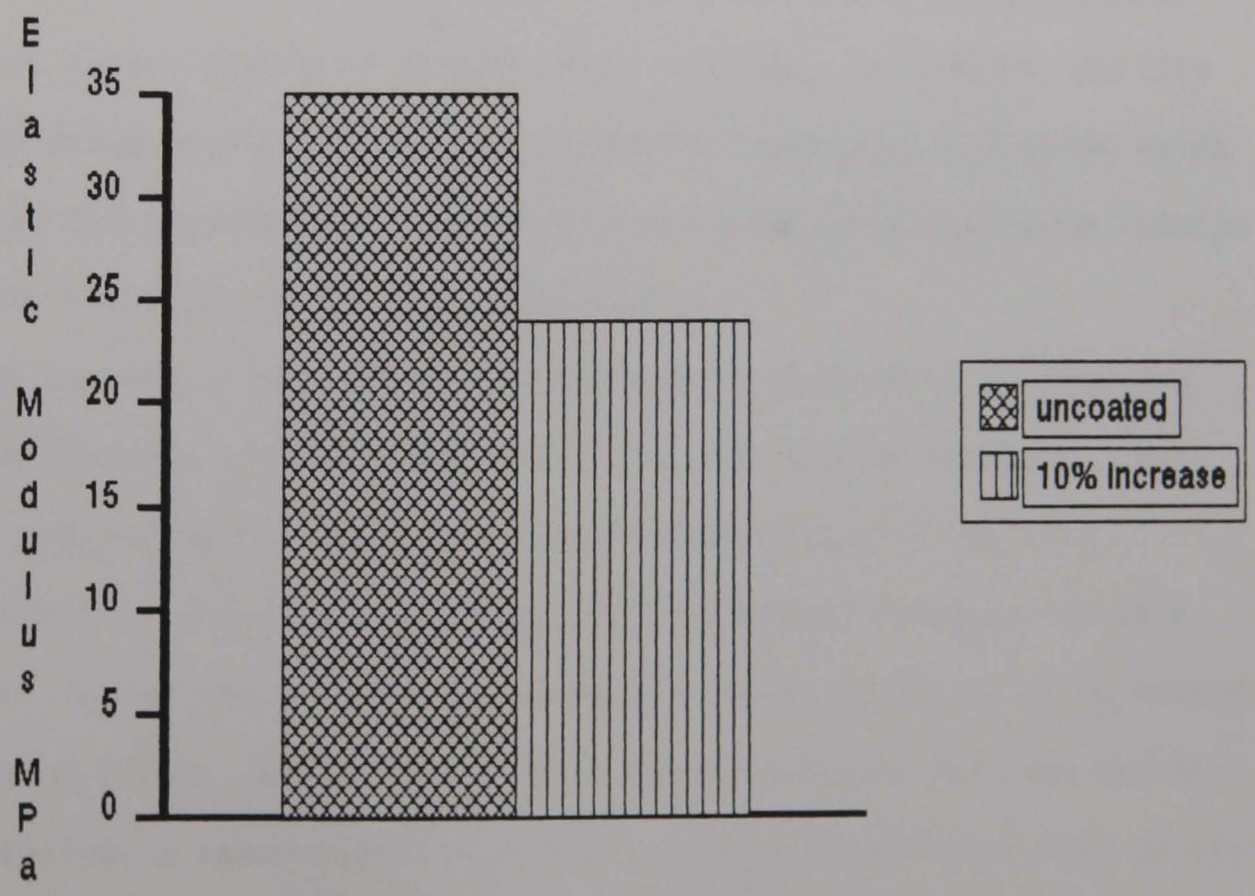


Figure 6.17. Effect of a film coat of Surelease (ethylcellulose) on the elastic modulus (MPa) of fluidised bed dried pellets containing 80%w/w ibuprofen.

As fracture occurs the point of application of force is dissipated throughout the pellet (Figure 6.19). The stress waves generated in the particle, the cause of the initial crack formation, release energy producing other regions of high stress resulting in new crack formation.

The application of stress to those pellet formulations exhibiting a relatively high elasticity tended on fracture, to result in a few relatively large particles and some fines. On fracturing more brittle pellet formulations however, the resultant product largely consisted of fines.

6.4. Conclusions.

Much quantitative and qualitative information is liberated by studying the effect of formulation factors and processing variables on the tensile properties of both placebo and ibuprofen pellets.

Of primary importance is the influence of the drying technique on the resultant mechanical properties of pellets containing excipients which are either poorly or freely water soluble. In summary, pellets prepared using extrusion and spheronisation technology and dried using fluidised bed methodology, exhibit greater elasticity and lower tensile strength than their tray dried counterparts.

The aqueous solubility of the excipients from which pellets are composed also has a significant effect on the tensile strength. For pellets containing a freely water-soluble excipient, it is not unreasonable to anticipate the formation of solute molecules of this component during the wet massing stage due to the addition of an aqueous granulating fluid. Water removal from these multiparticulates during drying following spheronisation of the material, would thus lead to the formation of solid bridges in the granules by fusion at the point of contact.

Figure 6.18. Photograph of a pellet on a stationary platen prior to stress application from the descending load.

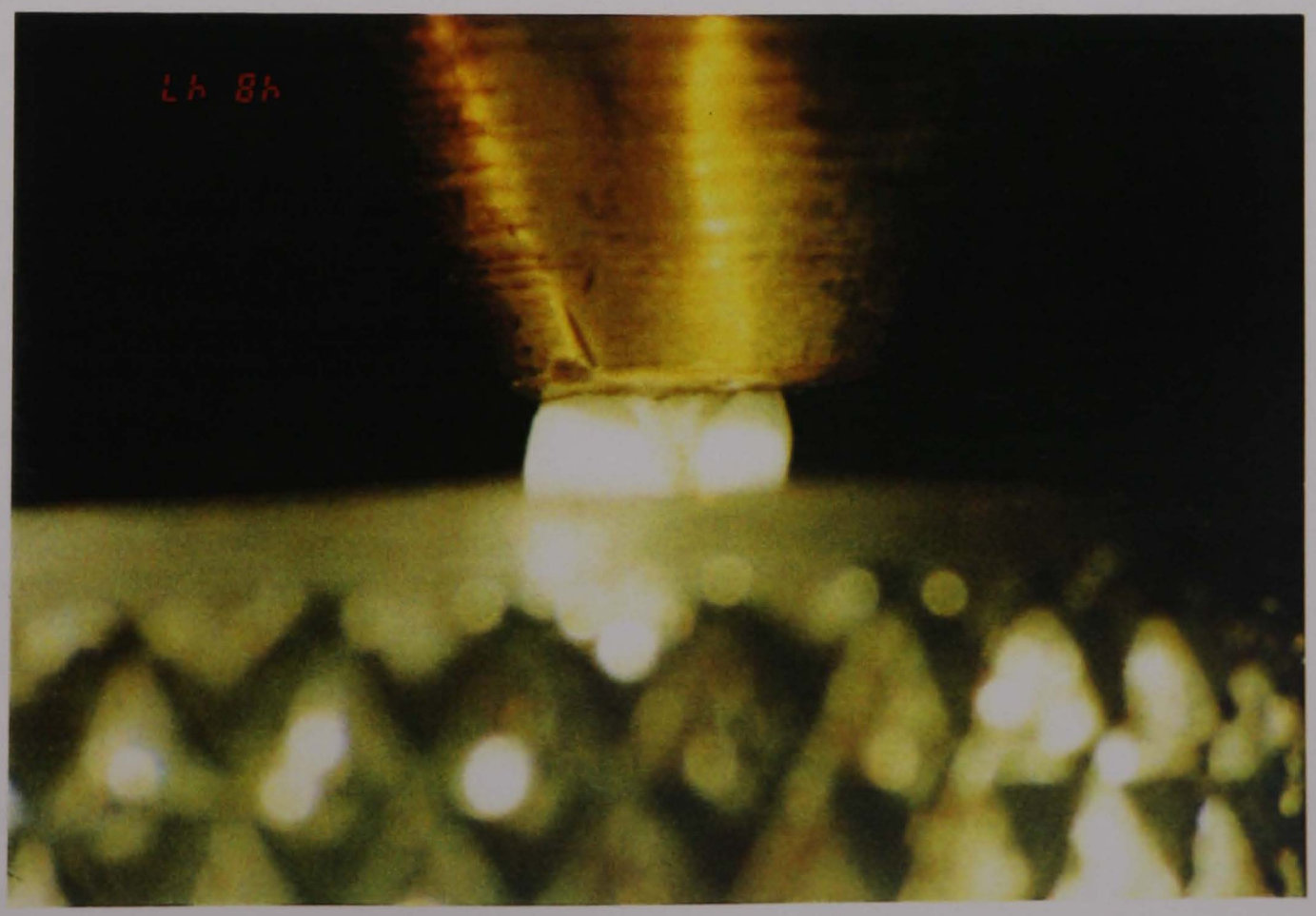


Figure 6.19. Photograph of the pellet during load application.

For solute particles (for example, lactose dissolved in the aqueous granulating fluid) crystallisation of the dissolved particles causes a greater degree of bonding and hence the formation pellets of greater tensile strength. This is supported by the relative tensile strengths of pellets containing 20%w/w microcrystalline cellulose with 80%w/w of either ibuprofen or lactose. Fluidised bed dried ibuprofen pellets exhibit a tensile strength which is only approximately 21 per cent of that of placebo pellets prepared using similar processing techniques.

The quantity of the spheronisation enhancer microcrystalline cellulose (Avicel PH101) in pellet formulations has a significant effect on the tensile strength and other tensile properties of pellets containing ibuprofen. An increase in the Avicel content of pellets and a corresponding decrease in the ibuprofen content therefore, has the effect of increasing pellet tensile strength (Figure 6.6) with a corresponding reduction in pellet elasticity (Figure 6.7). The presence of microcrystalline cellulose in pellet formulations serves not only to facilitate the production of high quality pellets, but in its capacity as a binder this excipient enhances the cohesion between the components of the blend, resulting in more robust pellets of greater tensile strength. For example, pellets containing only 20%w/w microcrystaline cellulose with 80%w/w ibuprofen required a mean force for fracture of 2.59N, compared with pellets containing 40%w/w microcrystalline cellulose which required a mean force of 4.91N. In addition, pellets containing only 20%w/w binder exhibited a mean elastic modulus of 35MPa, whilst pellets containing the higher per cent of binder (40%w/w) exhibited a mean elastic modulus of approximately 60MPa.

Grades of microcrystalline cellulose containing sodium carboxy-methylcellulose (sodium CMC), when incorporated into pellet formulations enhance the binding capacity of the inert component. As previously discussed, this facilitates the formation of products containing even

higher percentages of drug due to the additional binding capacity associated with such excipients. For any given drug loading however, the use of sodium CMC grades of microcrystalline cellulose (CL611 and RC591NF) leads to a more brittle product exhibiting enhanced tensile strength. Considering a specific example therefore: pellets containing 80%w/w ibuprofen and 20%w/w of Avicel PH101 required a mean force for particle fracture of 2.81N and exhibited an elastic modulus of 37MPa, whilst pellets of identical potency containing 15%w/w Avicel PH101 and 5%w/w Avicel CL611 (of which approximately 0.75% is NaCMC) exhibited a mean diametral strength of 5N and an elastic modulus of 43MPa; both formulations were tray dried in a hot air oven and were uncoated. It is therefore apparent that only minor changes in an uncoated pellet formulation will have significant ramifications in terms of the tensile properties of the resultant product.

The presence of a film coat applied by means of an aqueous polymeric dispersion of the polymethacrylates also influences the tensile strength and the elastic properties of ibuprofen pellets. Increasing the polymer loading has the effect of increasing the tensile strength of pellets whilst simultaneously enhancing pellet elasticity (characterised by a reduction in the elastic modulus, Figure 6.15). Elsewhere in this work, one of the consequences of increasing the tensile strength of pellets has been an increase in the elastic modulus (c.f. drying method and Avicel content). It is evident that the effect of a polymer coating surrounding a pellet core serves not only to enhance the tensile strength of ibuprofen-containing pellets but also to enhance the elasticity of such multiparticulates (Figure 6.15).

The effect of applying a film coating of Surelease (ethylcellulose) to ibuprofen pellets causes a reduction in diametral strength from 2.59N (uncoated) to 2.13N (pellets coated with a 10% weight increase of Surelease) and a corresponding increase in the pellet elasticity (Figure

6.17). This apparent reduction in tensile strength may be attributable to the penetration of water into the pellet core during the initial stages of the coating process; this is however only a postulation. This effect was not observed for pellets coated with polymethacrylate aqueous system. This conferred elasticity of Surelease-coated ibuprofen pellets is not wholly unexpected as a consequence of the quantified tensile properties of free-films of this polymer previously presented in Chapter 5. In summary, Surelease (ethylcellulose) free-films were found to exhibit extremely high instantaneous elastic compliance on the application of stress (approximately 20 x 10^{-8} Pa^{-1} compared with that of the polymethacrylate formulation of approximately 3.6 x 10^{-8} Pa^{-1}). Surelease free-films also exhibited the lowest Newtonian viscosity of all formulations studied (Figure 5.26) which is indicative of a greater tendency for permanent, non-recoverable, plastic deformation under applied stress.

An understanding of the tensile properties of uncoated pellets, coated pellets and free polymeric films was considered fundamental in facilitating the design of a monolithic tablet formulation comprising compacted polymer-coated pellets, in which the integrity of the pellet cores and the film coating were to be preserved. Chapter 7 considers fundamental tablet design and incorporates a quantitative study of pellet distribution within the tablet matrix and drug release from the pellets following compaction into tablets.

CHAPTER 7

DESIGN AND QUANTITATIVE EVALUATION OF A RAPIDLY DISINTEGRATING SUSTAINED RELEASE TABLET FORMULATION COMPRISING POLYMER COATED PELLETS

7.1. Introduction.

It is recognised that a multiple-unit sustained release dosage form presents a preferable alternative to a single-unit system for oral administration (Davis et al., 1984; Bechgaard and Nielsen, 1978; Ganderton, 1985). However, due to the physical limitations associated with the size of a hard gelatin capsule shell it has not been possible to administer a medium- to high-dose drug in the form of a sustained release multiparticulate delivery system. The aim of this work therefore was to design a tablet which on oral administration rapidly released intact polymer coated pellets with the integrity of the pellet core and the release retarding membrane being preserved.

The successful application of direct compression in pharmaceutical tabletting depends on the development of suitable excipients that are free flowing, highly compressible, water-soluble, physiologically inert and chemically compatible with the active ingredients. Spray-dried lactose exhibits these characteristics and it has been widely used as a direct compression excipient. There is however an associated problem with the use of lactose alone and that is the limited tablet diametral strength which may be achieved. The binding capacity of lactose is insufficient in facilitating the formation of tablets of low friability and of sustainable strength particularly in tablet formulations in which the percentage composition of the inert diluent phase is to be minimised. Garr and Rubinstein (1991) studied the properties of a direct compression excipient made of 25% cellulose and 75% lactose and showed that the cellulose-lactose excipient produces stronger tablets than those containing lactose alone.

Microcrystalline cellulose, the characteristics of which have been documented earlier in this work (Chapter 2), is highly cohesive and possesses favourable flow properties. This excipient facilitates the formation of extremely hard tablets exhibiting low friability and which

display relatively short disintegration times (FMC product literature. Avicel PH200, 1991). As the objective of this stage of the study was to design a tablet containing pellets of mean diameter 1mm and in order that the occurrence of segregation between the particles of the inert diluent blend and the active pellets was minimised, it was deemed necessary to elucidate a formula containing large size diluent particles, without necessitating an additional wet granulation process. The process of segregation within a blend is influenced by component particles exhibiting markedly differing particle size, shape and density. Avicel PH200 is a large particle size microcrystalline cellulose (average particle size 200 μm), the particle size specifications of which are given in Table 7.1.

Avicel Type	%	Particle Size Specification
PH101	1	not greater than 250 μm
	30	not greater than 75 μm
PH102	8	not greater than 250 μm
	45	not less than 75 μm
PH200	10	not less than 250 μm
	50	not less than 150 μm

Table 7.1. Particle size specifications of Avicel grades of microcrystalline cellulose.

Scanning electron microscopy of Avicel PH200 (Figure 7.1) indicates that this grade of microcrystalline cellulose is composed of relatively spherical aggregates; this is desirable in that not only is the particle size more favourable in respect of its potential for compression with 1mm diameter pellets, but also the more spherical shape of these particles, it is postulated, will reduce the tendency for particle segregation.

Figure 7.1. Scanning electron micrograph of Avicel PH200 microcrystalline cellulose (magnification x100).

The shape and particle size of this large particle size grade of microcrystalline cellulose, the manufacturers claim, enhances not only the flow properties and reduces the tablet weight variation, but favourable compressibility, tablet strength and content uniformity may be achieved.

The compressibility of microcrystalline cellulose is attributable to the hydrogen bonding in and between the cellulose structures of this excipient and also strong interparticulate bonding. The microcrystalline cellulose particles are held together by hydrogen bonding between hydroxyl groups on adjacent cellulose molecules, this accounts for the strength and coherence within the particles. Each particle is held together by a bonding of sub-particles rather than by entanglement of the elements comprising a particle; each particle is a coherent porous collection of small cellulose subunits. On compression, microcrystalline cellulose particles exhibit plastic deformation due to the presence of the slip planes and dislocations. Thus on the application of pressure, microcrystalline cellulose particles exhibit plastic deformation and bonds are formed which remain intact on the release of pressure. Rapid disintegration of tablets containing microcrystalline cellulose is

attributable to the hydrogen bond energy being significantly reduced as a consequence of the presence of water thus causing destruction of the mechanical interlocking of these cellulose particles.

No single ingredient is ideal as a direct-compression vehicle and therefore it was considered appropriate to blend excipients of differing properties together. A combination of lactose and microcrystalline cellulose offers two excipients which display fundamentally different fragmentary properties. Previously discussed is the fact that microcrystalline cellulose is highly compressible and consolidates by plastic deformation. In contrast however, the principal mechanism of lactose consolidation is by fragmentation.

Microcrystalline cellulose being highly compressible, produces hard tablets of low friability which are water insoluble. Lactose possesses relatively good compactibility and the resultant tablets are readily soluble in water. It is a possibility therefore that a blend of these two materials would result in a combination of the properties of the individual components.

The bonding created by the compression of a blend of lactose and microcrystalline cellulose therefore might reasonably be expected to involve a combination of plastic deformation associated with the hydrogen bonding between the microcrystalline cellulose particles affording physical strength to the resultant tablet and extensive fragmentation of the lactose component filling the void spaces during compression. The primary objectives of tablet design were therefore to ascertain the minimum quantity of inert diluent blend necessary for satisfactory tablet formation and optimisation of the ratio of the microcrystalline cellulose and lactose components, such that a rapidly disintegrating product of low friability could be achieved and in which the integrity of both the pellet core and the film coat were preserved.

Meggle lactose EP is pure, crystalline α-lactose monohydrate.

Various grades of Meggle lactose are available, exhibiting different particle size specifications. The largest particle size grade of lactose currently available is Meggle lactose, D10 grade. It is a coarse-crystalline product exhibiting favourable flow properties. The particle size specifications are given in Table 7.2.

%	Particle Size Specification
100	less than 800 µm
12 - 35%	less than 400 µm
max. 7%	less than 200 µm

Table 7.2. Particle size specification of Meggle D10 lactose EP.

Figure 7.2 shows a electron micrograph of D10 lactose, illustrating the coarse crystalline appearance of the product.

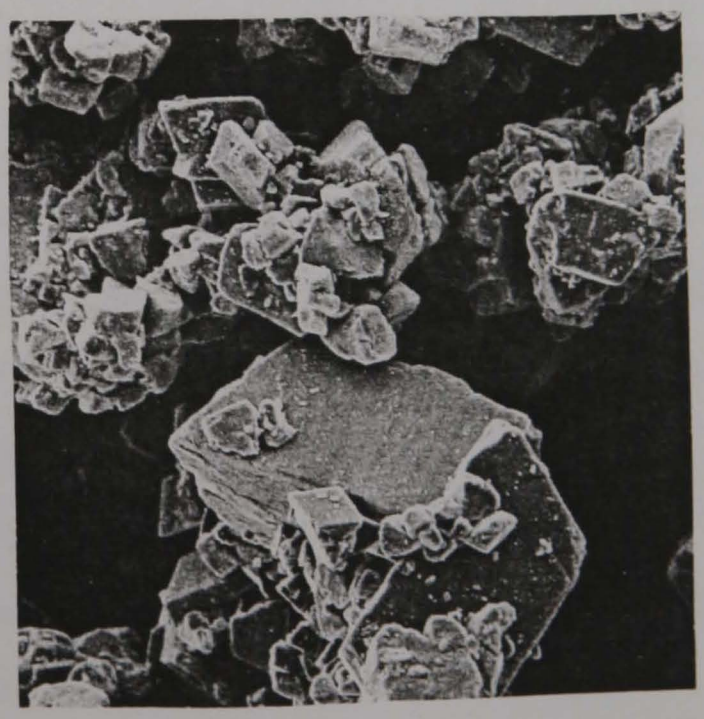


Figure 7.2. Scanning electron micrograph of Meggle D10 lactose EP (magnification x100)

7.2. **Methodology.**

7.2.1. Tablet design.

In an attempt to prevent segregation of the active pellets (mean diameter 1mm) from the diluent particles, the particle size and shape of the latter and the relative proportions in the blend were carefully optimised.

7.2.1.1. The role of placebo pellets and their mechanical properties relative to ibuprofen-containing entities.

It was postulated that the anticipated problems associated with pellet segregation from the diluent particles during compression, might be prevented or at least minimised by using placebo pellets as the inert tablet component. The theoretical concept involved designing a placebo pellet formulation which on consolidation exhibited fragmentary properties rather than plastic deformation and when compressed with polymer coated pellets containing ibuprofen, preferentially fractured into progeny particles thus facilitating tablet formation.

The aim was to design a placebo pellet formulation which exhibited fragmentation under applied load and which was mechanically less strong than the polymer coated entities. In theory at least segregation would be minimal. Placebo particles would mirror the physical properties of the ibuprofen-containing entities in respect of dimensions and shape and preferably density. To this end placebo pellets were prepared containing lactose and microcrystalline cellulose (Avicel PH101) using the technique of extrusion-spheronisation. The manufacturing plant and equipment is as described previously. Those placebo formulations manufactured are described in Table 7.3.

Excipient	%w/w (dry solids)	Granulating fluid	Comments
Avicel	100	purified water	undried - satisfactory dried - severe shrinkage poor quality, rock hard
Avicel lactose	50 50	purified water	appearance:satisfactory rock hard pellets
Avicel lactose	50 50	purified water:IPA 50:50	powdery, final product: less IPA required
Avicel lactose	50 50	purified water:IPA 80:20	appearance:satisfactory hard pellets
Avicel lactose	30 70	purified water	appearance:satisfactory rock hard pellets
Avicel lactose	20 80	purified water	appearance:satisfactory, evaluate mechanical properties
Avicel lactose	10 90	purified water	appearance:poor shape, more Avicel required to improve sphericity

Table 7.3. Placebo pellet formulations prepared using extrusion-spheronisation methodology.

The crushing properties of placebo pellets containing lactose PhEur (Pharmatose 200M = lactose monohydrate ground USP) 80%w/w and microcrystalline cellulose (Avicel PH101) 20%w/w (expressed as percent weight dry solids) were determined using the Single Particle Crushing Assembly described in Chapter 6. All other placebo pellet formulations described either resulted in poor quality spheres, or the mechanical strength of the pellets was greater than the evaluative capacity of the crushing assembly. Since the mechanical strength of those placebo pellet formulations was much greater than the ibuprofen-containing entities, these formulations were therefore discarded.

The relative mechanical strength of placebo pellets containing

80%w/w lactose with microcrystalline cellulose is discussed in 7.3.

7.2.1.2. Direct compression blend.

Coated ibuprofen pellets were blended in a Turbula mixer with Meggle D10 lactose EP and Avicel PH200 for 15 minutes (see Table 7.4 for quantities used). Magnesium stearate BP 0.5%w/w was then added to the bulk and blended for a further 10 minutes. The batch size of each blend was 250g.

7.2.2. Pellet compression.

The pellet/diluent blend was transferred to the hopper of a Manesty F3 (instrumented) tablet machine fitted with pillow shaped concave punches of dimensions 25mm x 9mm. The blend was then compressed into tablets using a range of compaction pressures, such that the minimum compression force needed to produce tablets of low friability, rapid disintegration (in which damage to the integrity of the coated pellets would be minimised) could be determined.

Table 7.4 summarises the tablet formulations studied. Details relating to the compaction forces, uniformity of weight, uniformity of content, diametral crushing force, tablet disintegration and *in-vitro* drug release are given subsequently in section 7.3.

blend ingredients	%w/w	% drug (uncoated pellets)	polymer	comments
pellets lactose Avicel PH102 Mg stearate	70 29.5 - 0.5	80	ERS/RL	insufficient filler; 29.5%w/w lactose not providing adequate cohesion for pellets
pellets lactose Avicel PH102 Mg stearate	70 14.5 10 0.5	80	ERS/RL	30%w/w diluent still insufficient even with extra binding capacity of Avicel
pellets lactose Avicel PH102 Mg stearate	60 39.5 - 0.5	70	Surelease	cushioning effect of 40%w/w diluent is more satisfactory; binder required
pellets lactose Avicel PH102 Mg stearate	60 29.5 10 0.5	70	Surelease	tabletting possible; friable on handling however with medium compaction pressures - increase % Avicel
pellets lactose Avicel PH102 Mg stearate	60 19.5 20 0.5	80	Surelease	appearance satisfactory at compaction force ≥ approx. 3kN smooth shiny tablets
pellets lactose Avicel PH102 Mg stearate	60 19.5 20 0.5	80	ERS/RL	appearance satisfactory at compaction force ≥ approx. 3kN; smooth shiny tablets
pellets lactose Avicel PH200 Mg stearate	60 19.5 20 0.5	80	ERS/RL	appearance satisfactory at compaction force ≥ 2.8kN; smooth shiny tablets
pellets lactose Avicel PH200 Mg stearate	60 19.5 20 0.5	80	Silicone elastomer 2:1	immediate elastic recovery on removal of applied stress; no resultant product
pellets lactose Avicel PH200 Mg stearate	60 19.5 20 0.5	80	Silicone elastomer 6:1	immediate elastic recovery on removal of applied stress; no resultant product

Table 7.4. Summary of pellet/diluent blends compacted into tablets.

7.2.3. Physical properties of compressed pellet formulations.

7.2.3.1. Diametral crushing strength.

Mean diametral tablet strength (longitudinal) was determined using a Schleuniger 4D Tablet Tester.

7.2.3.2. Tablet friability.

Tablet friability was determined using an Erweka Friabilator. The operating conditions involved testing samples of five tablets for a period of six minutes.

7.2.3.3. Tablet disintegration.

Disintegration testing was performed on six tablets using a BP 1988 basket-rack assembly and purified water at 37°C ± 2°C.

7.2.3.4. Uniformity of weight.

Preliminary adjustment of tablet weight was made for each pellet formulation and compaction pressure prior to compaction. Uniformity of weight of the resultant product was determined by weighing samples of ten tablets at each compaction pressure.

7.2.4. *In-vitro* drug release from compressed pellet formulations.

In-vitro drug release from compressed pellet formulations containing ibuprofen was performed over a period of 24 hours using the methodology described in section 4.2 of Chapter 4. Comparative drug release profiles from coated pellets and from a compacted pellet formulation are presented in section 7.3.

7.2.5. Uniformity of content.

Content uniformity of compressed pellet formulations was determined by ascertaining the infinity value of % ibuprofen released as a

consequence of *in-vitro* dissolution testing. Pellets were crushed after the 24 hour dissolution run *in situ* (ie. in the dissolution vessels) and the absorbance values recorded.

7.2.6. Qualitative study of the compression process and pellet integrity using microphotography.

Pellets were released from tablets by disintegration of the matrices as described in 7.2.3.3. Following release, pellets were recovered from the disintegration tubes by filtration and allowed to dry under ambient conditions of temperature and humidity. Ambient conditions were employed for the drying procedure such that pellet shrinkage might be minimised. After the leaching of ibuprofen from these cores it is important to note that only 20% by weight of the original core formulation remains; it was anticipated that elevated drying temperatures of pellet cores consisting of a skeletal network of microcrystalline cellulose surrounded by a polymeric membrane may be causative of unnecessary product deformation and shrinkage.

Released pellets were then examined microscopically with particular attention being made to the particle shape and any deformation and damage caused as a consequence of the compaction process.

Microphotographic illustrations of coated pellets prior to and after release from the tablet matrix and embedded in the tablet core are presented in section 7.3.

7.2.7. Quantitative evaluation of pellet distribution within the tablet matrix by image analysis.

A quantitative evaluation of the distribution of pellets within the compacted pellet tablet formulation was made using an Eltime III Image Analysis System. This facilitated a study of the tendency of the components of the tablet blend to undergo segregation. Samples of

ibuprofen-containing pellets were coated and stained with a 0.1%w/w aqueous solution of Green S, a water soluble dye used in the food industry. Tablets were prepared using the method and equipment discussed previously. The distribution of stained pellets embedded in the tablet diluent using this technique was presented by a monochrome display of grey, representing stained pellets on a white background. Samples of tablets were individually analysed in respect of pellet distribution on the tablet surface, the side view and cross-section. Microphotographic illustrations of stained pellets forming the tablet surface and embedded in the tablet core are presented in section 7.3.

7.3. Results and Discussion.

The process of pellet formation leads to a densification of materials. This factor together with the high concentrations of drug which are feasible for extruded-spheronised multiparticulates, renders it possible to present ibuprofen (a low potency/high dose drug) as an oral sustained release pellet preparation.

7.3.1. Mechanical properties of placebo pellets.

The objective of designing placebo pellets exhibiting fragmentary consolidation on the application of minimal applied load was to facilitate the compression of a blend of mechanically weak diluent particles and polymer coated actives such that the placebo pellets would preferentially fracture forming the tablet matrix around **intact** polymer coated pellets. A fundamental design feature underlying this theory was that the polymer coated particles must exhibit plastic deformation on the application of stress and greater physical strength than the placebo pellets.

It was postulated that by designing placebo pellets of similar size and shape to the drug-containing entities, the blending process would

enable a sustainable random mix to be achieved with negligible tendency for particle segregation during processing. This would have ramifications in respect of the uniformity of weight and content of the resultant compacted pellet formulations. To this end various placebo pellet formulations were prepared using the techniques described previously. Table 7.3 shows those pellet formulations prepared. The virtues associated with the use of microcrystalline cellulose in extrusion-spheronisation pelletization processing is well documented in the literature and has been discussed earlier in this work (section 2.3). Pellets containing microcrystalline cellulose alone required large volumes of granulating fluid (3kg of Avicel PH101 required 3500ml of Purified water BP during the massing stage in order that good quality extrudate and spheres could be produced). On removal of this large volume of water during drying, particle shrinkage occurred to such an extent that dried pellets resembled granules rather than spheres; they were also extremely hard. Various placebo formulations were therefore prepared using a combination of lactose and microcrystalline cellulose. Not unreasonably it was anticipated that these two significantly different excipients in combination might yield a product which exhibited physical properties characteristic of the component materials. That is to say, on consolidation of a lactose-microcrystalline cellulose pellet one might anticipate a degree of brittle fracture and plastic deformation (of the uncoated pellet) depending on the ratio of the component excipients and the load applied. Suffice to indicate that whatever the anticipated theory underlying the behaviour of such particles on the application of stress, all formulations containing lactose and microcrystalline cellulose exhibited greater mechanical strength than the polymer coated actives. This is attributable to the nature of the bonding between component materials during drying. Lactose is freely soluble in water (the granulating fluid) and therefore it is not

unreasonable to expect that, during the wet processing stages of product manufacture, solute molecules of lactose will be formed and a consequence of drying will be crystallisation of the dissolved particles, greater bonding and a mechanically stronger product due to crystalline bridge formation. Conversely ibuprofen-containing pellets. in which the drug is virtually insoluble in the granulating fluid are physically less strong; negligible drug solvation and crystalline bond formation will occur and therefore active pellets containing a poorly water soluble drug less physical strength.

It became evident therefore that placebo pellets containing a high lactose component exhibited greater physical strength than the drug-containing entities due to strong crystalline bonding in the former. In addition, placebo pellets containing a high microcrystalline cellulose content, by virtue of the inherent binding capacity of this material, were exceedingly hard.

The ability of lactose to dissolve in the aqueous granulating fluid appeared to be the fundamental problem. Solvation of lactose particles and subsequent crystalline bond formation during drying was yielding a product exhibiting greater mechanical strength than the drug laden pellets. It was therefore postulated that partial replacement of the aqueous component with a non-aqueous fluid, for example isopropyl alcohol IPA (frequently used in tablet granulations where water is inappropriate for example where the drug or another excipient is susceptible to hydrolysis), might enable the preparation of relatively soft placebo pellets which would preferentially fracture during tablet compression. Placebo pellet formulations in which some of the aqueous granulating fluid was substituted with IPA however still exhibited greater mechanical strength than those prepared using water alone.

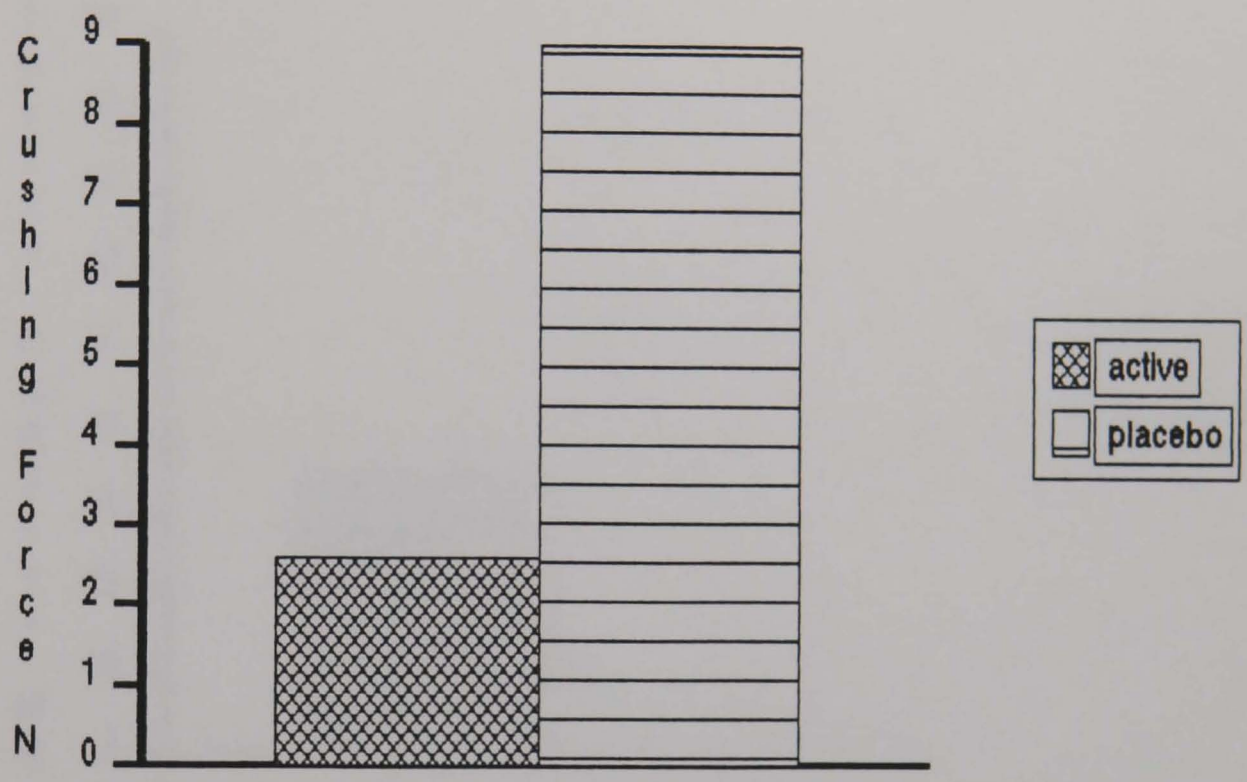


Figure 7.3. Relative mechanical strength of fluidised bed dried pellets containing 80%w/w ibuprofen or lactose with 20%w/w microcrystalline cellulose (Avicel PH101).

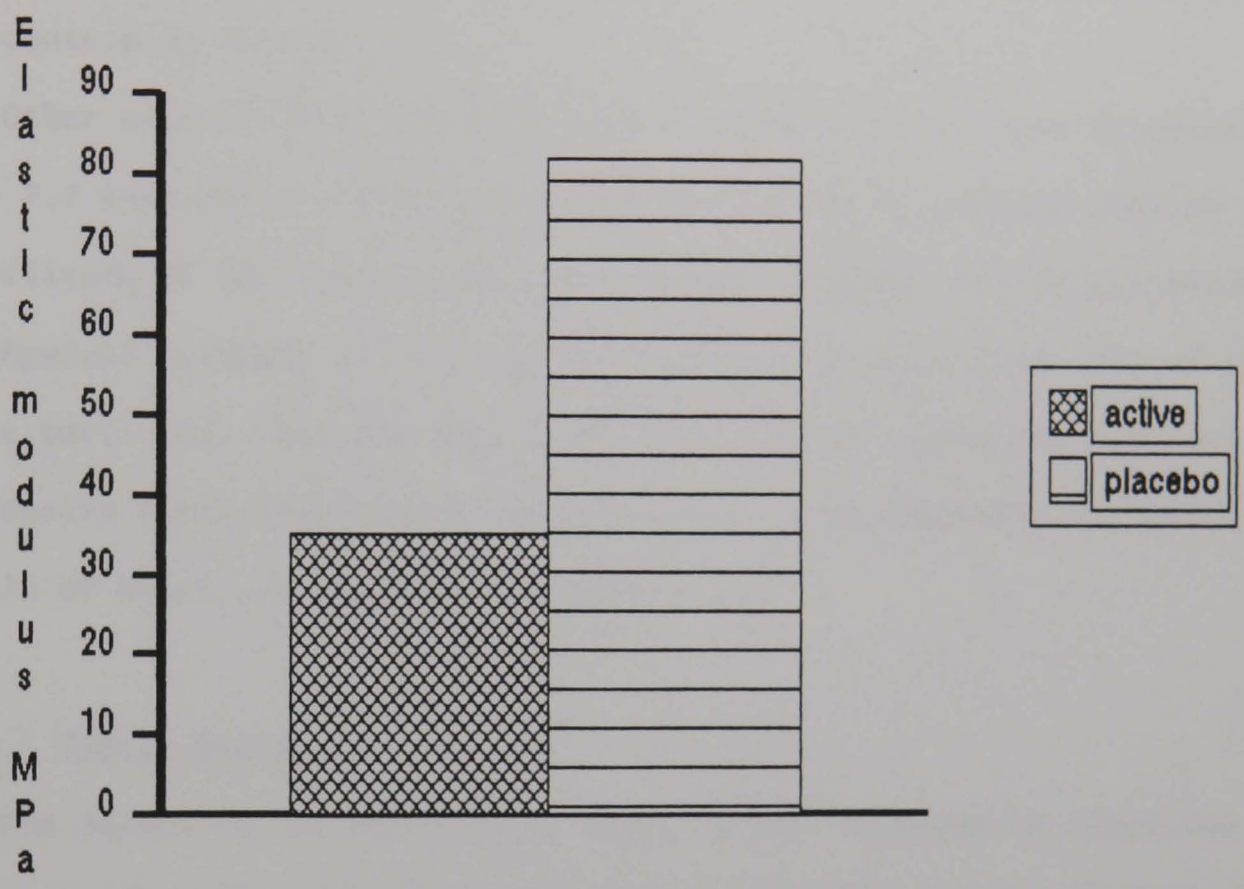


Figure 7.4. Relative elastic moduli (MPa) of fluidised bed dried pellets containing 80%w/w ibuprofen or lactose with 20%w/w microcrystalline cellulose (Avicel PH101).

Figures 7.3 and 7.4 show the relative mechanical strengths and elastic moduli of fluidised bed dried pellets containing 80%w/w ibuprofen or lactose with 20%w/w microcrystalline cellulose (Avicel PH101); both products were wet massed using purified water and similar processing variables and equipment as described previously (section 2.2). These figures illustrate that the placebo pellets require a three-fold force for particle fracture and exhibit significantly less elasticity than the drug-containing entities.

Other placebo pellet formulations studied and which are detailed in Table 7.3 required a crushing force which was quantitatively outside the capabilities of the Single Particle Crushing Assembly and in any event the physical strength of these pellets was far greater than that of the active particles. Further work therefore involved designing a direct compression blend composed of large particle size component excipients, details of which are discussed subsequently.

7.3.2. Tablet Design.

The objective in designing an inert direct compression blend was to enable the formation of a mechanically robust tablet of low friability, which was rapidly disintegrating *in vitro* yielding multiparticulates in which the integrity of the pellet core and the film coating remained intact.

Tables 7.5 to 7.10 inclusive summarise the more successful compressed pellet formulations prepared.

% drug in core formulation	70%w/w		
film coating	Surelease (10 + 1 % weight increase)		
%w/w inert diluent: Meggle D10 lactose EP Magnesium stearate BP	40%w/w 39.5% 0.5%		
compression force	1.12kN	1.74kN	2.02kN
diametral crushing strength	21.6 N	50.0 N	66.6 N
friability	100 %	100 %	100 %
BP disintegration (seconds)	255	300	345
target weight (g) ± 5%	2.117g (2.011 - 2.223g)		
uniformity of weight mean (g) standard deviation (SD) (g) % relative SD	 2.164 0.018 0.81	 2.179 0.007 0.30	 2.173 0.008 0.38
appearance: powdery surface appearance			
COMMENTS: tablets exceedingly friable in respect of friability test and on handling; binder required to reduce friability and increase tablet strength at lower compression forces. Increasing compression force has little effect on tablet strength.			

Table 7.5. Compressed pellet formulations (i) containing 800mg ibuprofen and 40%w/w inert diluent blend.

% drug in core formulation	70%w/w		
film coating	Surelease (10 + 1 % weight increase)		
%w/w inert diluent: Meggle D10 lactose EP Avicel PH102 Magnesium stearate BP	40%w/w 29.5% 10.0% 0.5%		
compression force	1.44kN	3.02kN	5.19kN
diametral crushing strength	37.2 N	69.6 N	104.9N
friability	100 %	100 %	45.4 %
BP disintegration (seconds)	150	150	150
target weight (g) ± 5%	2.117g (2.011 - 2.223g)		
uniformity of weight mean (g) standard deviation (SD) (g) % relative SD	 2.127 0.006 0.28	 2.170 0.012 0.55	 2.197 0.017 0.77
appearance: smooth shiny uniform surface characteristics (compression force ≥ 3kN)			
COMMENTS: tablet friability unsatisfactory; there is an apparent reduction in disintegration time associated with the presence of Avicel.			

Table 7.6. Compressed pellet formulations (ii) containing 800mg ibuprofen and 40%w/w inert diluent blend.

% drug in core formulation	80%w/w		
film coating	Surelease (10 + 1 % weight increase)		
%w/w inert diluent: Meggle D10 lactose EP Avicel PH102 Magnesium stearate BP	40%w/w 19.5% 20.0% 0.5%		
compression force	1.97kN	3.06kN	4.94kN
diametral crushing strength	66 N	115 N	126 N
friability	100 %	24.3 %	5.5 %
BP disintegration (seconds)	60	60	90
target weight (g) ± 5%	1.852g (1.759 - 1.945g)		
uniformity of weight mean (g) standard deviation (SD) (g) % relative SD	 1.871 0.013 0.70	 1.911 0.006 0.29	 1.916 0.002 0.12
COMMENTS: tablet appearance satisfactory at compaction pressures ≥ approx. 3kN (smooth shiny uniform surface characteristics). Increased rate of disintegration with increased microcrystalline cellulose content.			

Table 7.7. Compressed pellet formulations (iii) containing 800mg ibuprofen and 40%w/w inert diluent blend.

% drug in core formulation	80%w/w		
film coating	Eudragit RS/RL30D (4.5% weight increase)		
%w/w inert diluent: Meggle D10 lactose EP Avicel PH102 Magnesium stearate BP	40%w/w 19.5% 20.0% 0.5%		
compression force	2.34kN	3.19kN	4.99kN
diametral crushing strength	83 N	118 N	155 N
friability	100 %	21.3 %	1.98 %
BP disintegration (seconds)	45	60	75
target weight (g) ± 5%	1.742g (1.655 - 1.829g)		
uniformity of weight mean (g) standard deviation (SD) (g) % relative SD	 1.809 0.0064 0.36	 1.798 0.0166 0.92	 1.801 0.0032 0.18
appearance: smooth shiny uniform surface characteristics (compression force ≥ approx. 3kN)			
COMMENTS: increasing diametral crushing strength and decreasing tablet disintegration time with increasing Avicel content.			

Table 7.8. Compressed pellet formulations (iv) containing 800mg ibuprofen and 40%w/w inert diluent blend.

% drug in core formulation	80%w/w		
film coating	Eudragit RS/RL30D (4.5% weight increase)		
%w/w inert diluent: Meggle D10 lactose EP Avicel PH200 Magnesium stearate BP	40%w/w 19.5% 20.0% 0.5%		
compression force	1.15 kN	2.80kN	4.75kN
diametral crushing strength	32.3 N	148 N	198 N
friability	100 %	5.76 %	1.74 %
BP disintegration (seconds)	60	60	90
target weight (g) ± 5%	1.742g (1.655 - 1.829g)		
uniformity of weight mean (g) standard deviation (SD) (g) % relative SD	 1.744 0.0067 0.38	 1.767 0.0055 0.31	 1.777 0.0035 0.20
appearance: smooth shiny uniform surface characteristics (compression force ≥ 2.8kN)			
COMMENTS: large particle size microcrystalline cellulose (Avicel PH200) enhances diametral crushing strength; reduces tablet weight variation; reduces friability and improves tablet appearance.			

Table 7.9. Compressed pellet formulations (v) containing 800mg ibuprofen and 40%w/w inert diluent blend.

% drug in core formulation	80%w/w		
film coating	Silicone Elastomer 2:1 (10 % weight increase)		
%w/w inert diluent: Meggle D10 lactose EP Avicel PH102 Magnesium stearate BP	40%w/w 19.5% 20.0% 0.5%		
compression force	5 kN	5 kN	5kN
diametral crushing strength			
friability			
BP disintegration (seconds)			
target weight (g) ± 5%	1.833g (1.741 - 1.925g)		
uniformity of weight mean (g) standard deviation (SD) (g) % relative SD			
appearance: no product			
COMMENTS: at compression force of 5kN (max) it was not possible to produce tablets. Instantaneous elastic recovery of the coated pellets occurred immediately on removal of applied stress, resulting in tablets which crumbled into the original blend from which they were intended to be composed after release from the die.			

Table 7.10. Compressed pellet formulations (vi) containing 800mg ibuprofen and 40%w/w inert diluent blend.

Within the course of designing a direct compression diluent blend suitable for compression with spherical particles of mean diameter 1mm the following facts were elucidated.

On compression of pellets and a diluent consisting solely of lactose, increasing the compression force does not necessarily result in a proportionate increase in the diametral crushing strength of the tablets. It is not possible to form very strong tablets where lactose is the single or main component of the diluent (Tables 7.5 and 7.6).

The incorporation of a binder for example microcrystalline cellulose into the diluent blend renders it possible to produce stronger tablets; a further effect of the incorporation of or an increase in the percentage of the microcrystalline cellulose present, is a reduction in the tablet disintegration time (cf. Tables 7.5, 7.6 and 7.7). Briefly increasing the quantity of microcrystalline cellulose in the diluent formulation increases the tablet strength at a given compaction pressure and enhances the rate of disintegration of the tablet.

Compaction of pellets with lactose as the sole component of the diluent formulation, results in a product which is exceedingly friable to handle and which is unable to sustain its integrity as a consequence of the friability test (Table 7.5).

The use of a large particle size grade of microcrystalline cellulose (Avicel PH200; mean particle size 200 micrometers) leads to a reduction in the friability of the tablets at a given compression force. This may be explained by the fact that segregation may be occurring in blends containing the PH102 grade rather than the PH200 grade of Avicel. Therefore those tablets containing the PH102 grade (Table 7.8) effectively contain less binder per tablet than those compressed with Avicel PH200 (Table 7.9) as a consequence of containing disproportionately more lactose than is indicated by the diluent formula.

Pellets coated with both polymethacrylate and ethylcellulose

polymers compacted satisfactorily into tablets with respect to appearance. Those pellets coated with the silicone elastomer formulations however exhibited such a degree of instantaneous elastic recovery following release from the tablet die that they literally disintegrated into their component excipients prior to compression. This effect was observed even for those pellets subjected to compression forces in excess of 5kN (Table 7.10); this should be compared with those ibuprofen pellets coated with a 4.5% weight increase of the Eudragit RS/RL30D formulation which displayed a diametral crushing strength of 198N when compacted under a force of 4.75kN.

7.3.3. Detailed study of the properties of the optimised compressed pellet formulation.

The optimised diluent blend formulation consisted of lactose 19.5%w/w (Meggle Lactose EP D10 grade mean particle size 500µm), microcrystalline cellulose 20%w/w (Avicel PH200) and magnesium stearate BP (Table 7.9). The minimum quantity of inert diluent blend which was necessary to fill the void volume within such a tablet comprising polymer coated pellets (such that the integrity of the pellets was maintained and yet a mechanically strong tablet of low friability was produced) was found to be 40%w/w. Less than 40%w/w diluent blend resulted in a product ranging from friable (<40%w/w >30%w/w) to incomplete tablet formation (<30%w/w inert diluent blend).

This ibuprofen compressed pellet formulation rapidly disintegrates *in-vitro* releasing apparently intact coated pellets within 90 seconds (compression force 4.75kN).

7.3.3.1. *In-vitro* drug release from polymer coated compressed pellets compared with non-compressed pellets.

In order to quantify the extent of pellet damage it is necessary to

consider the effect of compaction on the *in-vitro* drug release profiles from those multiparticulates which have been subjected to the compression process and those which have not.

Figure 7.5 shows the effect of the compression process on drug release. It is evident that slight damage is caused to pellets as a consequence of compaction; this is highlighted by an increase in the rate of drug release from compacted, compared with non-compacted entities. The extent of physical damage of the film coat resulting from pellet compaction may be quantified by examining these differences in the *in-vitro* release profiles. Figure 7.6 is the square root time plot for ibuprofen pellets coated with a 4.5% weight increase of the polymethacrylate aqueous dispersion (see Table 7.9 for formulation details). Figure 7.6 illustrates a largely linear release for both free pellets and those presented as tablets. It is postulated that although pellet compaction may enhance the rate of drug release by causing physical damage to the film coat of some pellets particularly those at the tablet surface, it appears to have little effect on the mechanism of drug release; first-order release kinetics are apparent at this level of polymer coating both before and after pellet compression. Also worthy of note in respect of the error bars shown in Figure 7.5 is the fact that whilst drug release from non-compacted pellets is exceptionally uniform, a consequence of pellet compaction is an apparent increase in the range of per cent drug released in replicate *in-vitro* tests.

It is apparent from Figures 7.5 and 7.6 that by increasing the force of compaction from 2.80kN to 4.75kN there is negligible effect on the damage inflicted to these multiparticulates. Consequences of a significant increase in the compaction force include an increase in diametral crushing strength, a reduction in product friability, enhancement of product appearance but no apparent additional damage to these sub-units. This indicates at this stage that under these

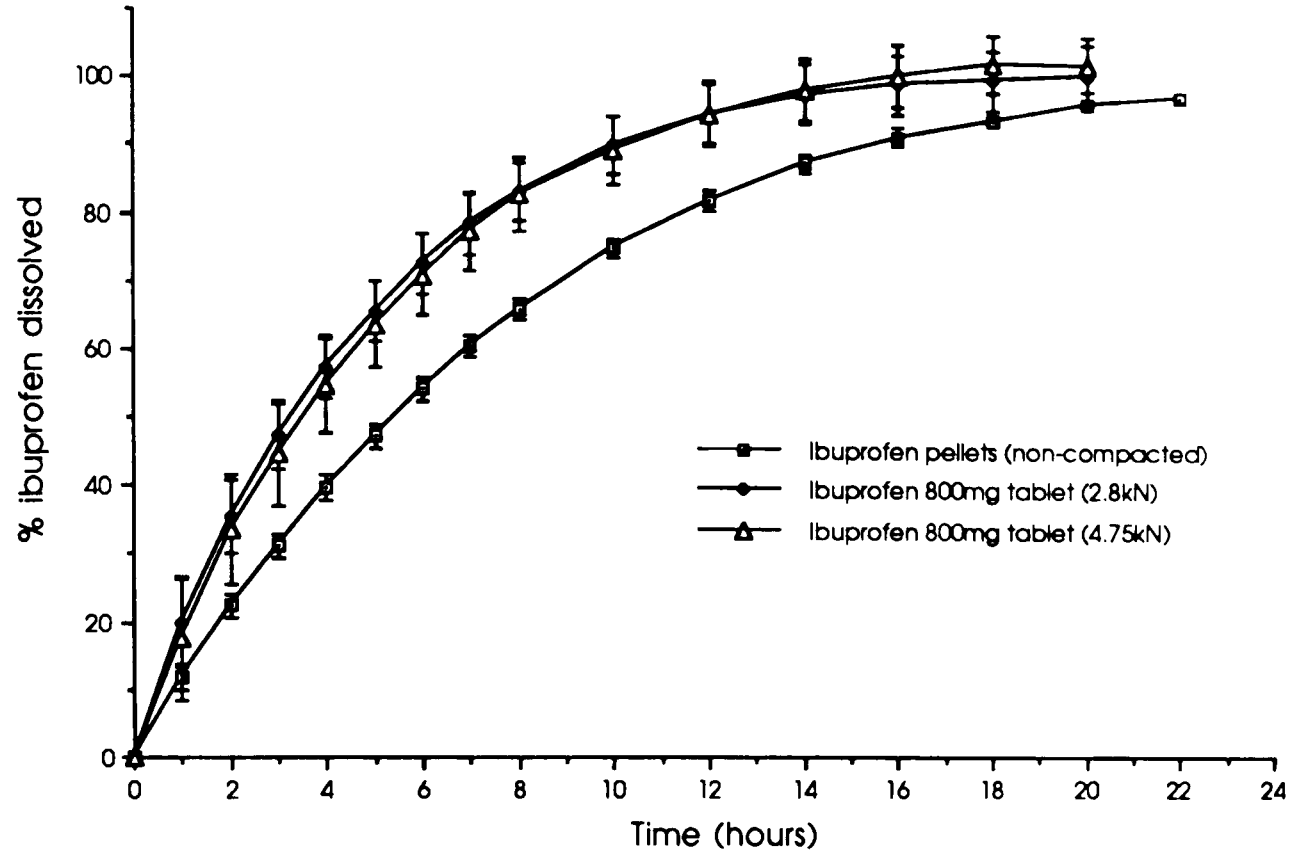


Figure 7.5. *In-vitro* drug release from compacted and non-compacted pellet formulations containing 800mg ibuprofen.

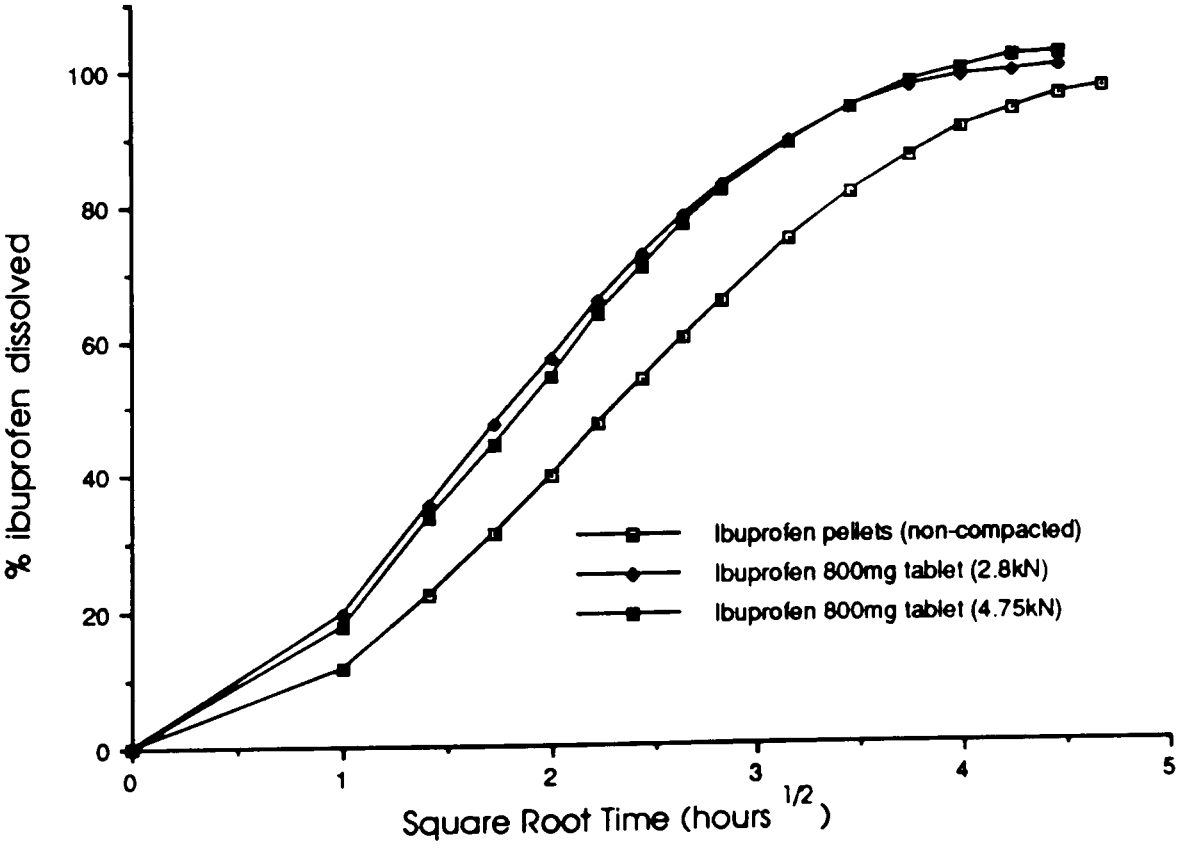


Figure 7.6. Drug release versus square root time profile for compacted and non-compacted pellets formulations containing 800mg ibuprofen.

conditions impairment of either the integrity of the film coat or the pellet core is not related to the magnitude of the compaction force but to the actual act of pellet compaction.

7.3.3.2. Uniformity of content.

The properties of the optimised tablet formulation containing 800mg ibuprofen in the form of compacted polymer coated sustained release pellets are summarised in Table 7.11. Despite the apparent random packing arrangement of coated pellets within these tablets as highlighted by the microphotographic evidence and image analysis data presented subsequently, the uniformity of content of these compacted pellet formulations indicates that the variation in ibuprofen content falls within a target specification value of 5% relative standard deviation (RSD); the inference being that under the pilot scale conditions in which these tablets were prepared, segregation of the diluent blend from the active pellets does not appear to be a problem.

7.3.3.3. Qualitative study of the compression process and pellet integrity using microphotography.

Microphotographs of coated pellets prior to compaction (Figure 7.7) and those released from the tablet following disintegration (Figures 7.8 and 7.9) show that some pellets appear to undergo a degree of physical deformation as a consequence of the compaction process.

Investigations to determine the nature of the damage to the film coat were carried out using scanning electron microscopy (SEM) and evidence is presented subsequently illustrating that limited damage is being incurred by some pellets, particularly those at the tablet surface which are unprotected from contact with the punches during compaction by the tablet diluent.

% drug in core formulation	80 %w/w
film coating	Eudragit RS/RL30D (4.5% weight increase)
<u>%w/w inert diluent:</u> Meggle D10 lactose EP Avicel PH200 Magnesium stearate BP	 40.0%w/w 19.5%w/w 20.0%w/w 0.5%w/w
compression force	4.75 kN
diametral crushing strength	198 N
friability	1.74 %w/w
BP disintegration	90 seconds
<u>uniformity of weight</u> mean (g) standard deviation (SD) (g) % relative SD	 1.7767 0.0035 0.2
<u>uniformity of content</u> mean standard deviation (SD) % relative SD	 102.4% 4.33 4.22
appearance	smooth shiny surface
drug release	(see Figs. 7.5 and 7.6)

Table 7.11. Summary of physical properties of the optimised compressed pellet formulation containing 800mg ibuprofen.

7.3.3.4. <u>Quantitative evaluation of pellet distribution within the tablet matrix by image analysis.</u>

Image analysis was performed on tablet surface, cross-section and side sections (Figure 7.11). Table 7.12 quantifies the ratio of that area occupied by the stained pellets to that by the diluent blend in respect of these three parameters.

ratio black/white	surface	side view	cross-section
mean	1.7020	0.5886	1.3779
n	20	20	20
SD	0.3999	0.2063	0.7884
%RSD	23.5	35.1	57.2
area occupied by pellets(%)	62.99 ± 14.8	37.05 ± 13.0	57.95 ± 33.2

Table 7.12. Summary of data showing the distribution of sustained release ibuprofen pellets in tablets containing 800mg ibuprofen.

The high relative standard deviation (RSD) values obtained by image analysis of the various tablet sections indicate that the internal structure of these tablets comprising compacted polymer coated pellets exhibits a somewhat random packing arrangement. Figure 7.11 shows computer images of samples studied. It is evident that some pellets are not buffered from contact with each other by the diluent as a consequence of the compaction process.

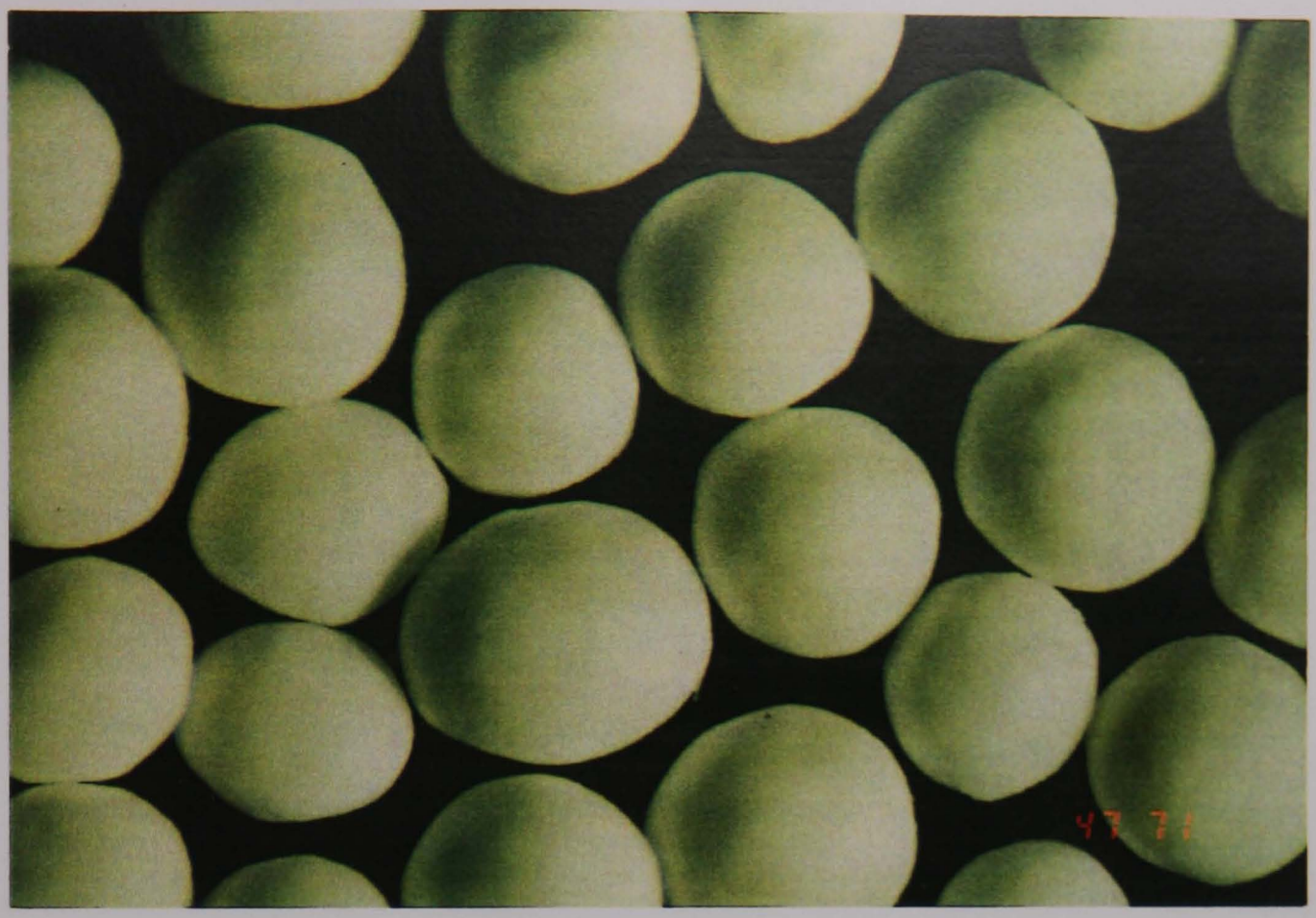


Figure 7.7. Microphotograph of polymer coated pellets prior to compaction into a tablet matrix; magnification x25

Figure 7.8. Microphotograph of polymer coated pellets after release from a tablet matrix; magnification x25

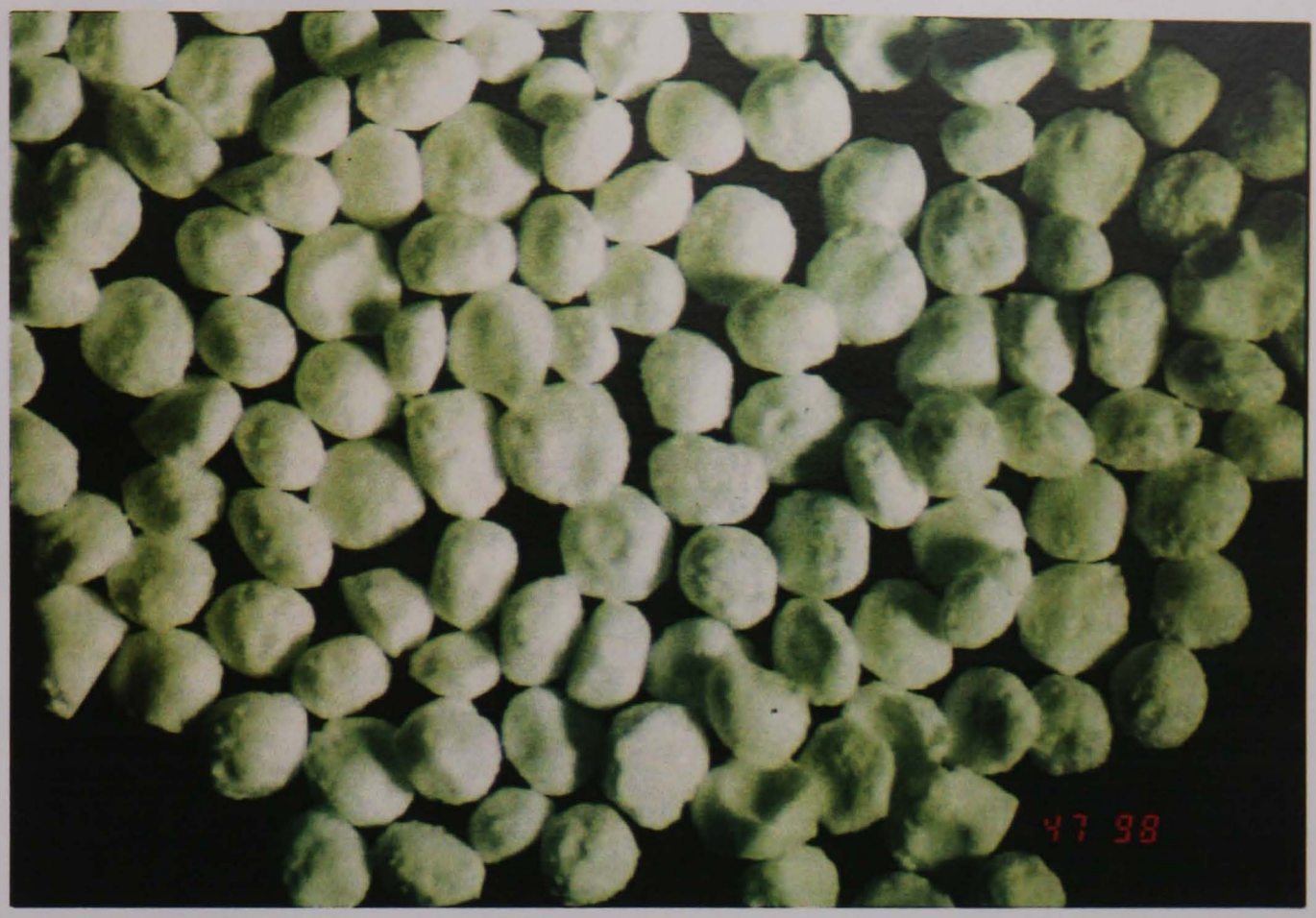
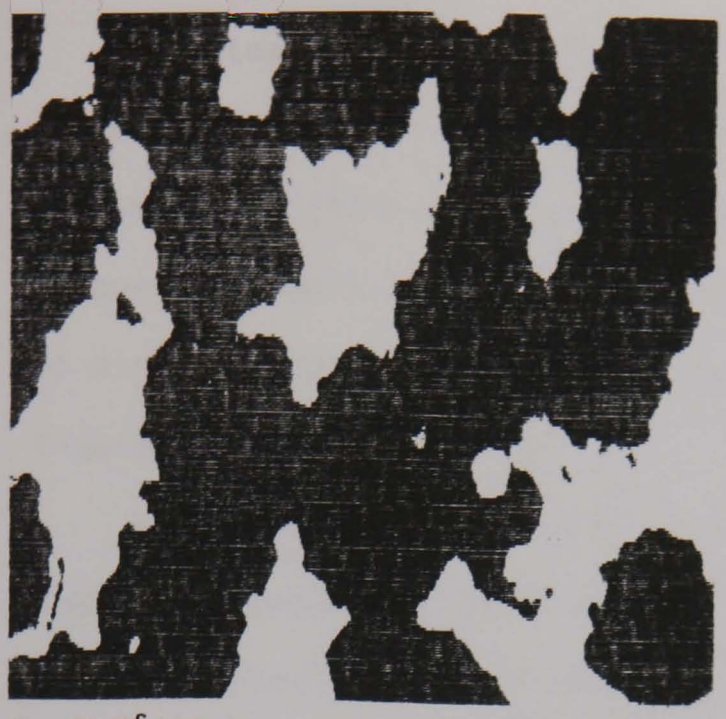


Figure 7.9. Microphotograph of polymer coated pellets <u>after release</u> from a tablet matrix; magnification x10

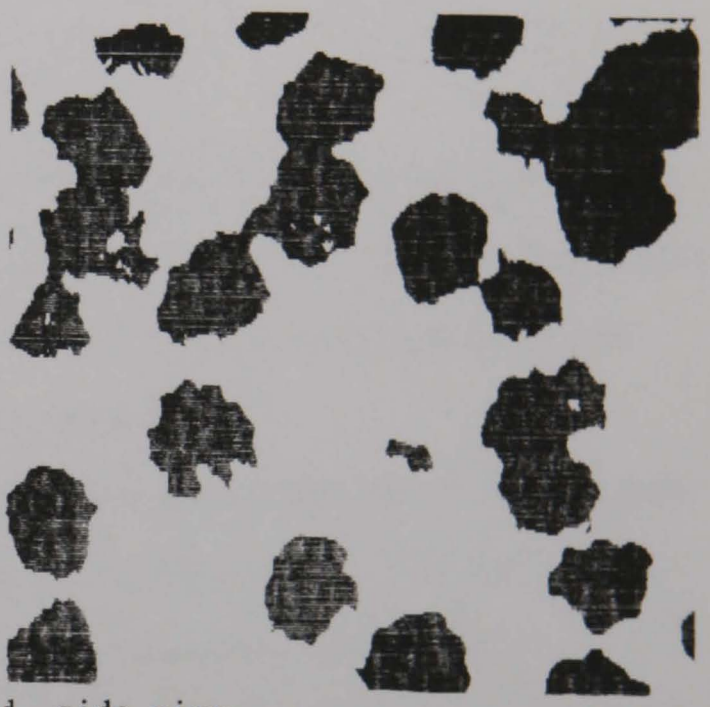
Figure 7.10. Microphotograph of a tablet cross-section comprising compacted polymer coated pellets; magnification x15



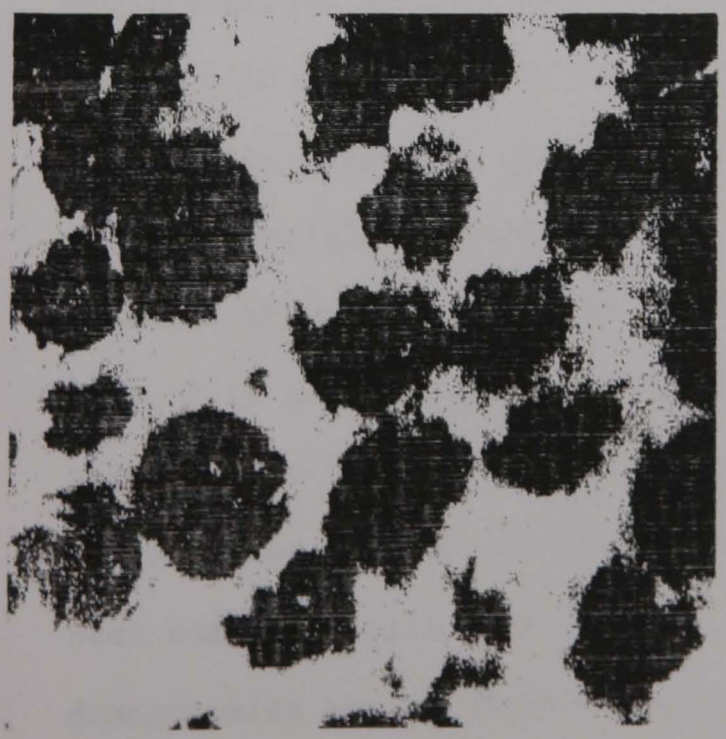
a. surface

b. surface

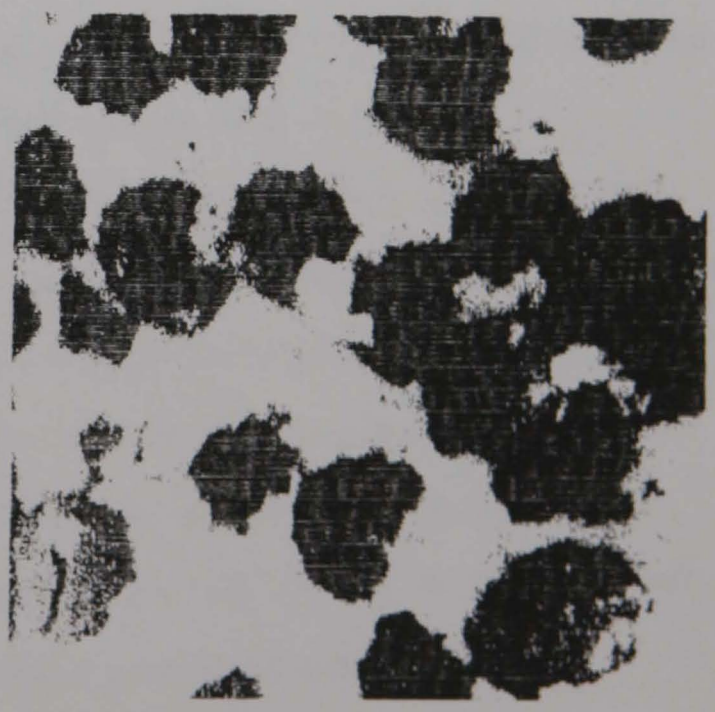
c. side view



d. side view



e. cross-section



f. cross-section

Figure 7.11. Computer generated images of tablet sections;(2cm=1mm)

Disintegration of the tablet matrix however yields discrete, visibly intact single entities. Figures 7.11a and 7.11b. show the effect of compaction on those pellets forming the tablet surface. They appear to be more susceptible to physical deformation and damage, as a consequence of direct contact with the tablet punches. This is highlighted by Figures 7.12 and 7.13.

Microphotographs of tablet cross-sections reinforce the postulation that those pellets forming a tablet surface have a greater tendency towards physical deformation (Figure 7.16). It would appear that although this unstructured packing arrangement might indicate that there may be a tendency for segregation to occur, this does appear to be the case.

Figures 7.8 and 7.9 indicate that the effect of the compaction process on the pellet core integrity appears to be of little consequence; there is however an unquestionable influence on the smoothness of the pellet surface and the quality of the spheres.

The effect of compaction on the nature and integrity of the release retarding polymeric membrane is shown in Figures 7.18, 7.19 and 7.20. The surface characteristics of this particle under different magnifications must be compared with that illustrated in Figure 4.25. Figure 4.25 is a scanning electron micrograph (SEM) of the surface of an identically processed ibuprofen pellet coated with the same polymethacrylate aqueous dispersion prior to compaction; there is no evidence of holes or craters of the magnitude of those evident in Figures 7.18, 7.19 and 7.20 which represent those pellets which have been subjected to the compaction process. It must be stressed however that these latter figures are not representative of all pellets which have been compacted into tablets; they illustrate the nature of the physical damage which may be incurred by pellets as a consequence of the compaction process.

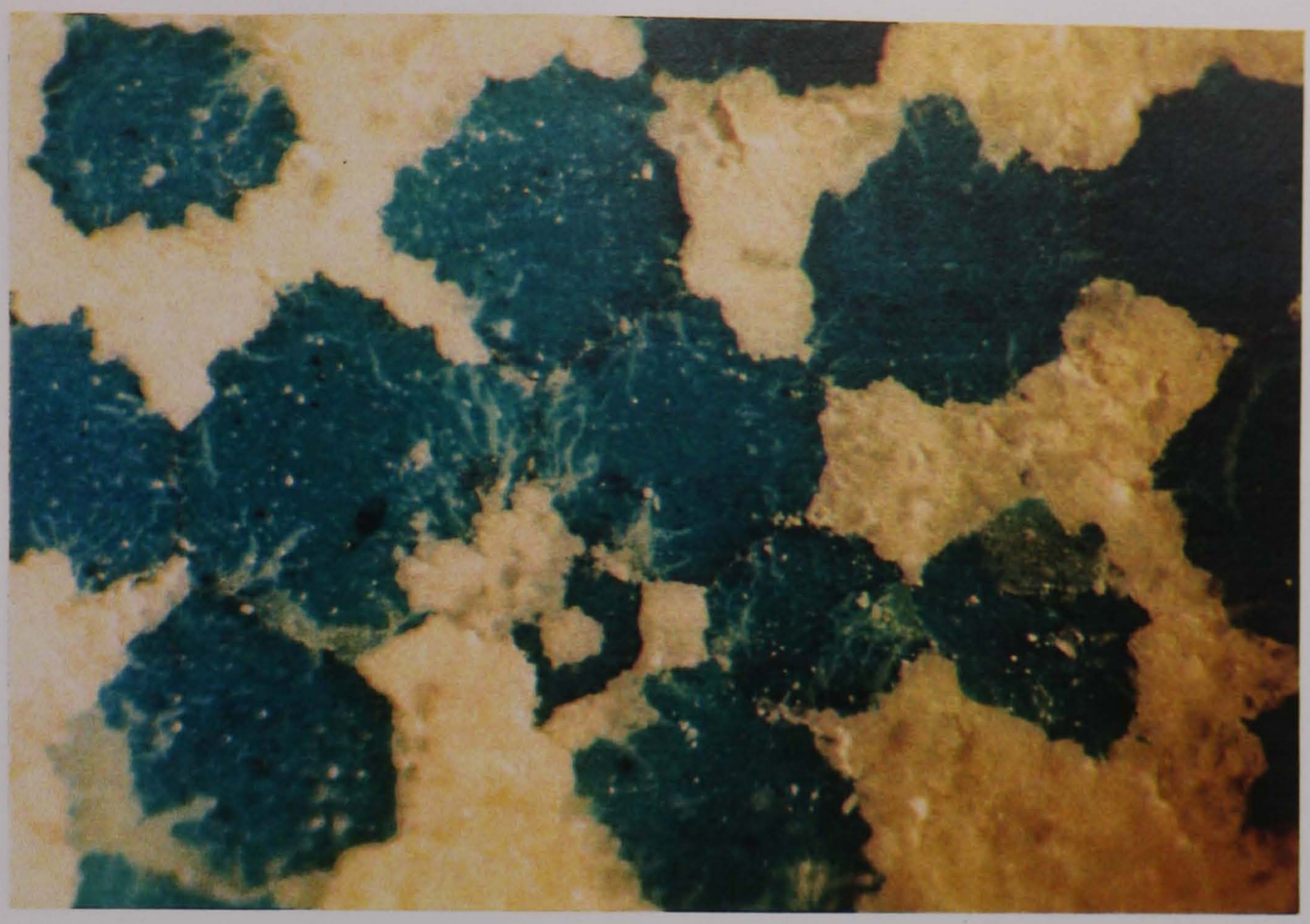


Figure 7.12. Microphotograph of exposed stained pellets embedded in the diluent blend (surface); magnification x50

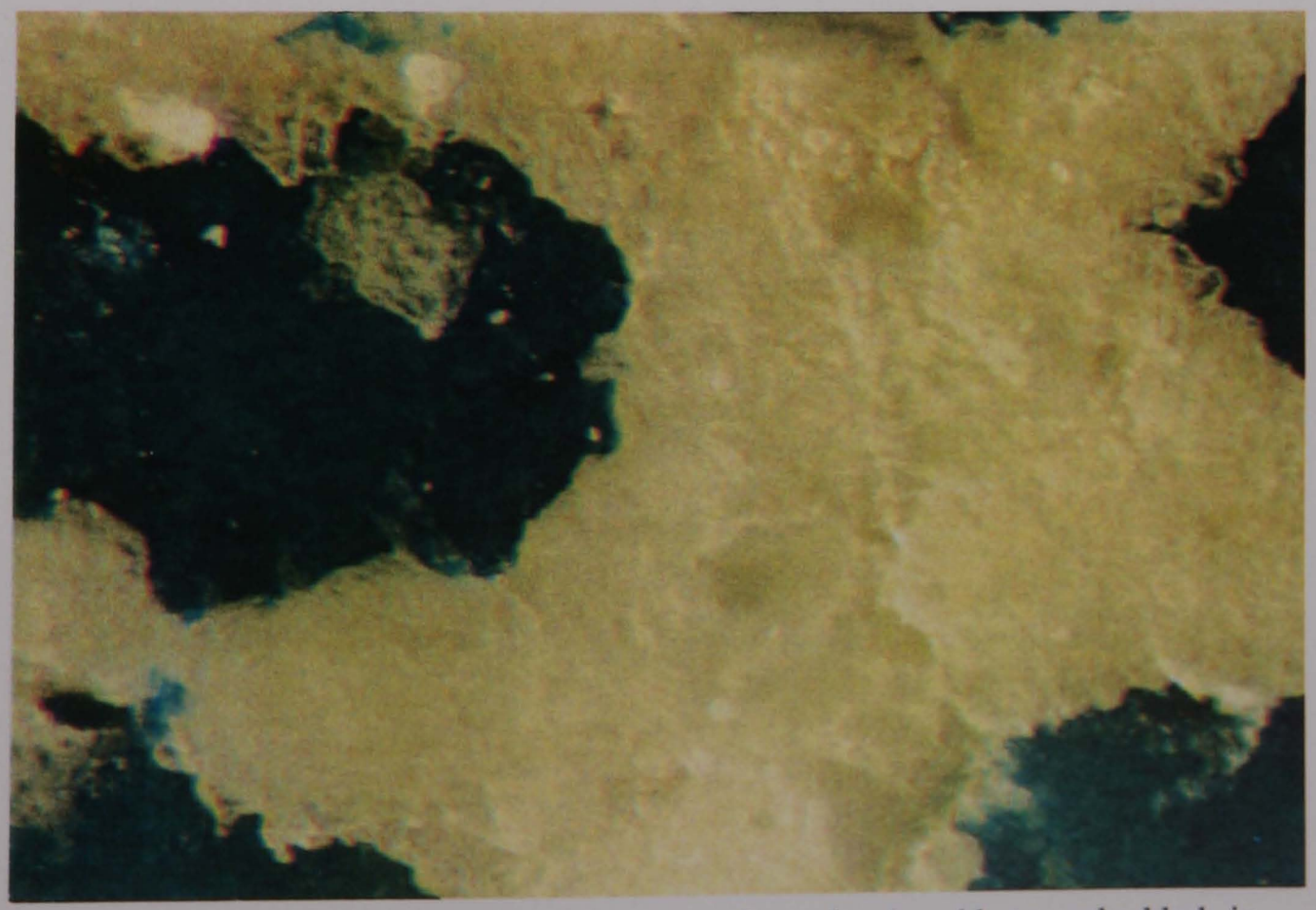


Figure 7.13. Microphotograph of exposed stained pellets embedded in the diluent blend (surface); magnification x100

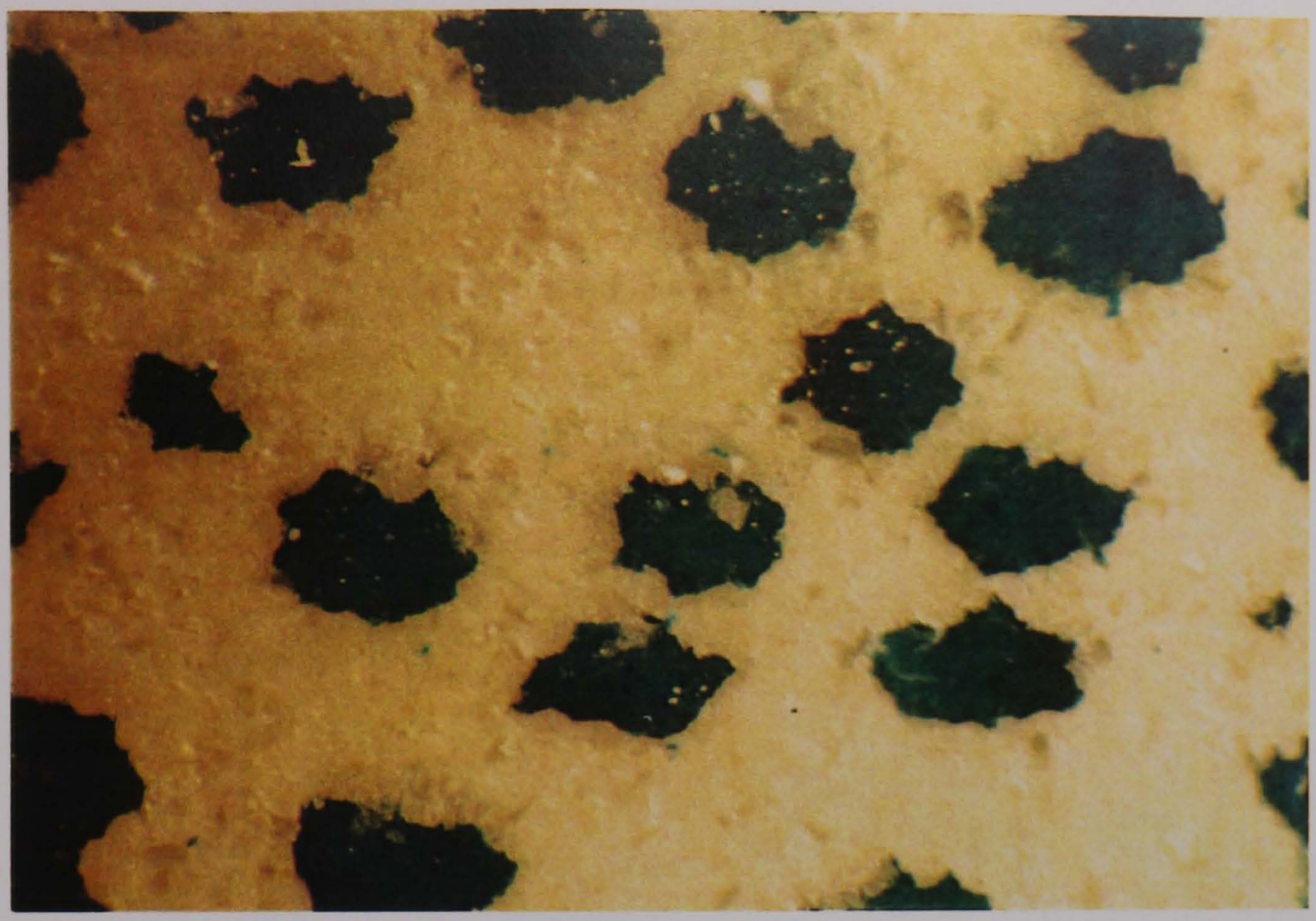


Figure 7.14. Microphotograph of exposed stained pellets embedded in the diluent blend (side view); magnification x50

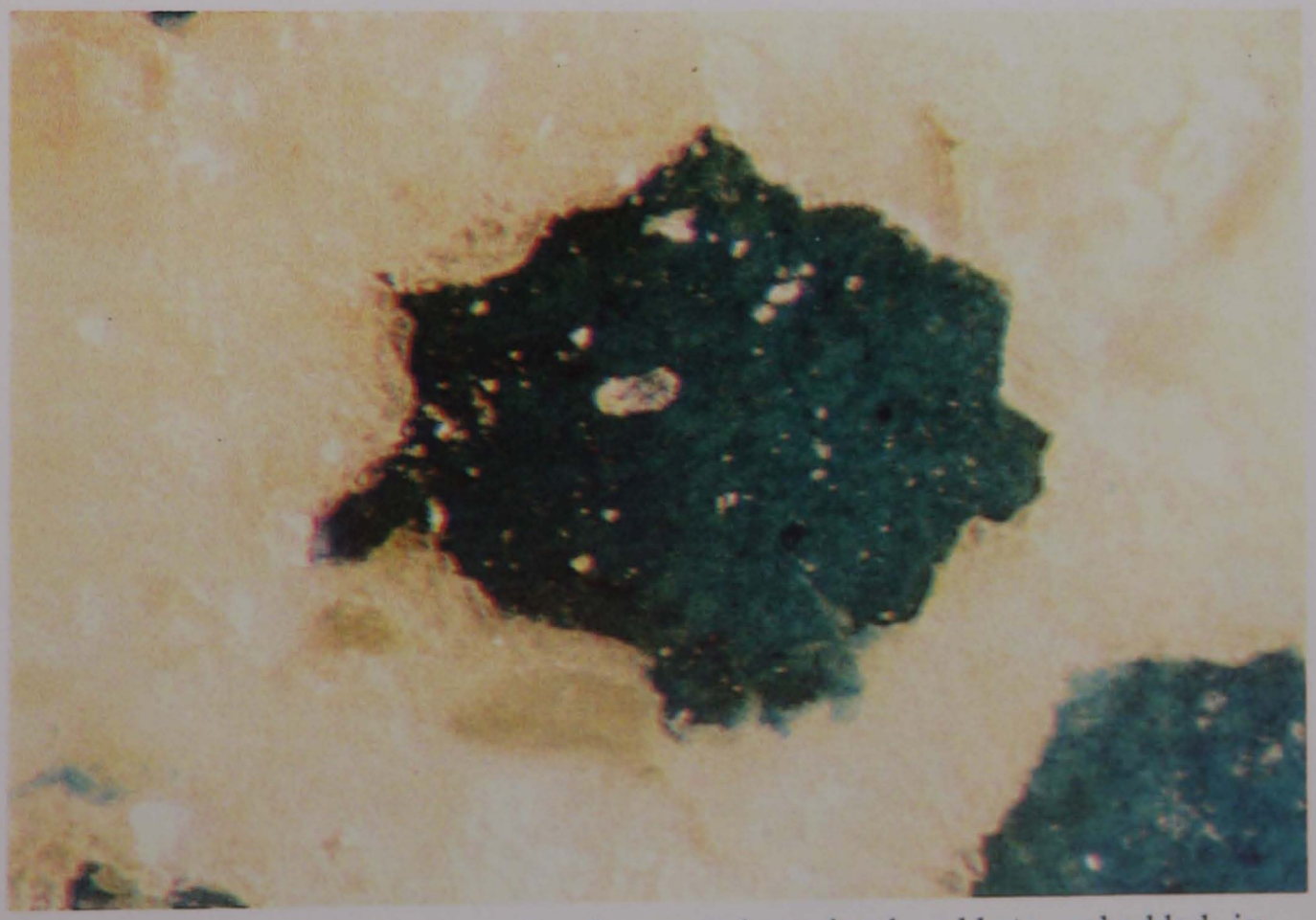


Figure 7.15. Microphotograph of exposed stained pellets embedded in the diluent blend (side view); magnification x150

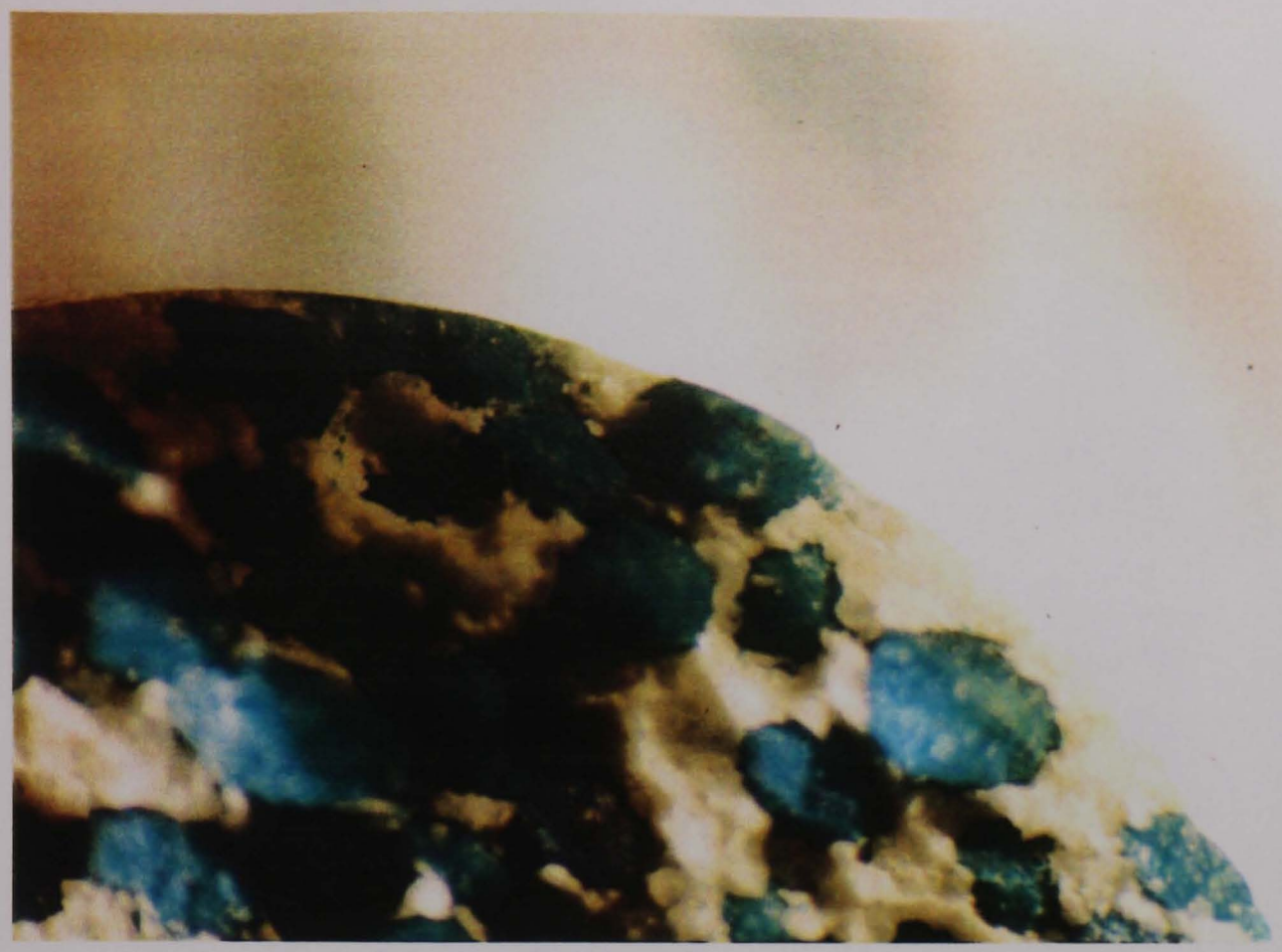


Figure 7.16. Microphotograph of exposed stained pellets embedded in the diluent blend (cross-section); magnification x20

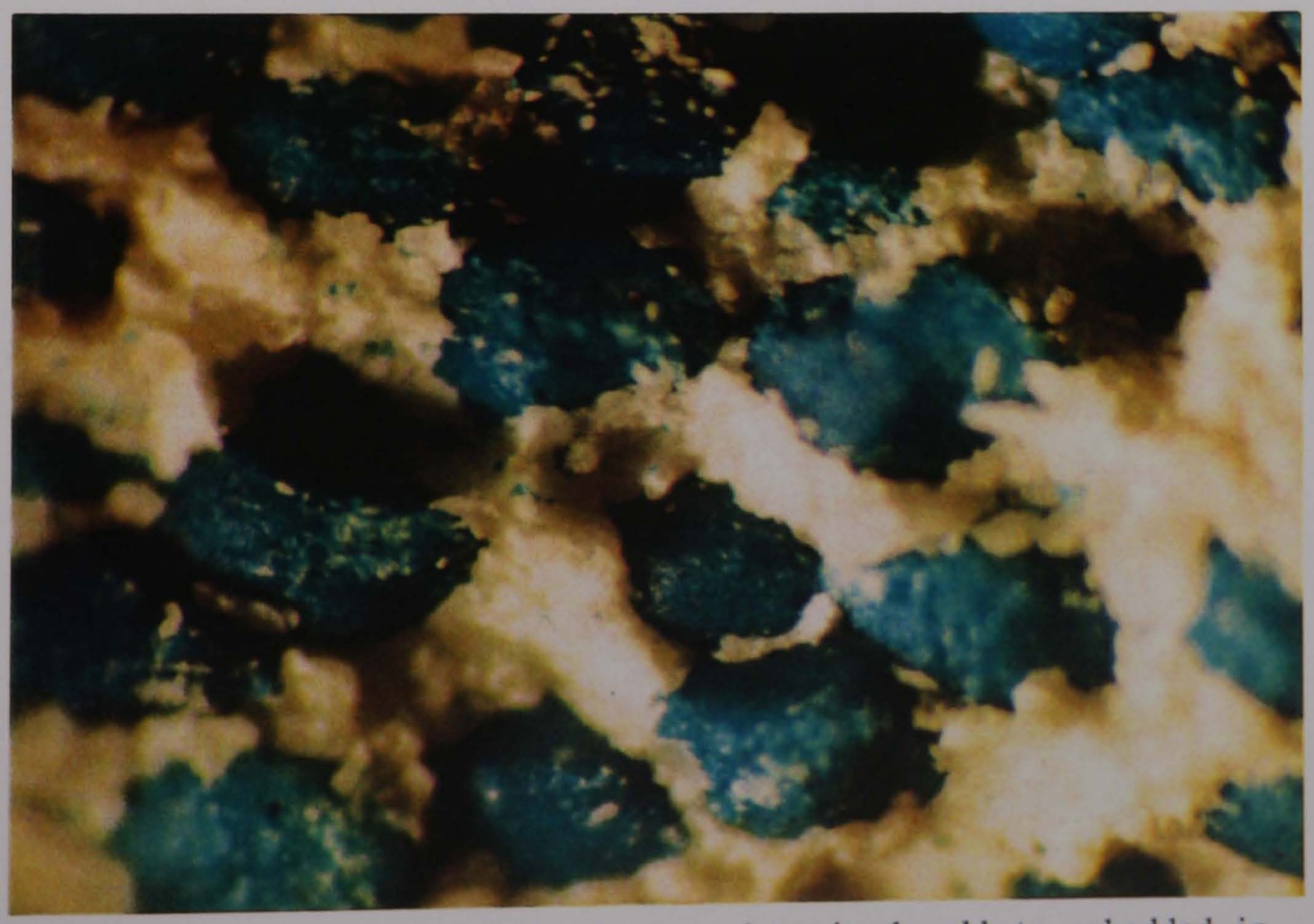


Figure 7.17. Microphotograph of exposed stained pellets embedded in the diluent blend (cross-section); magnification x40

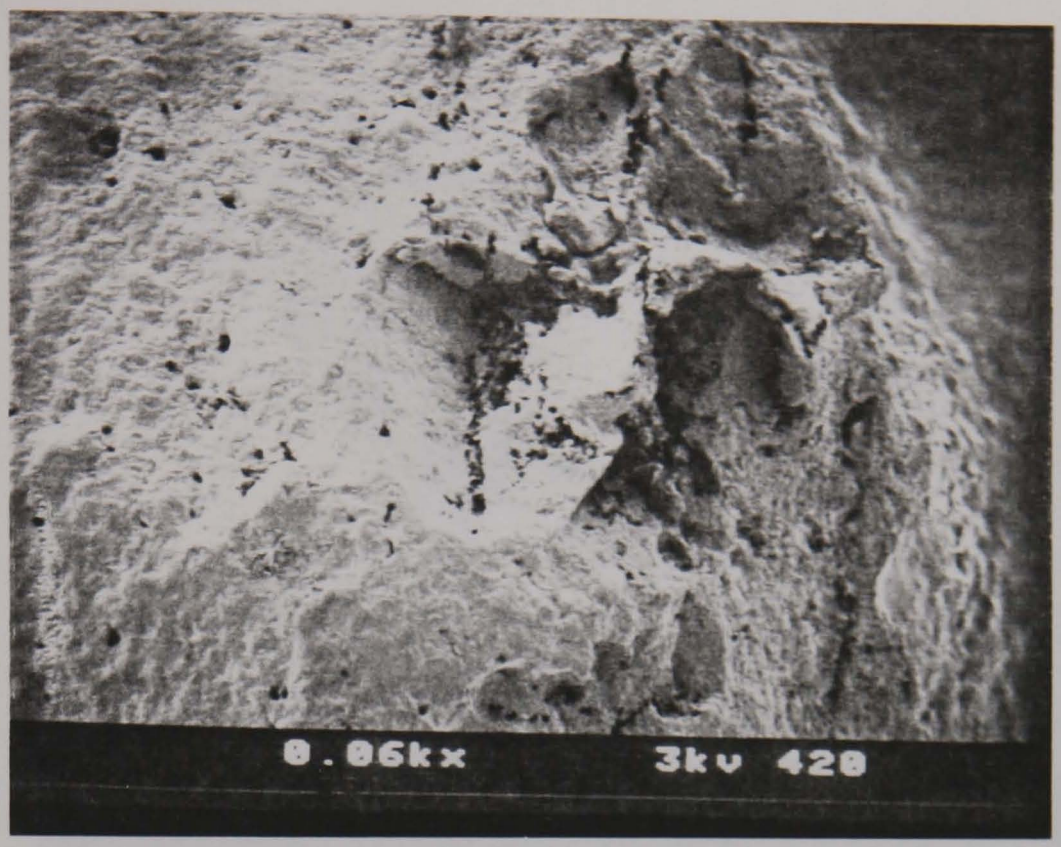


Figure 7.18. SEM of the surface of a pellet coated with ERS/RL30D after release from a tablet matrix; magnification x240

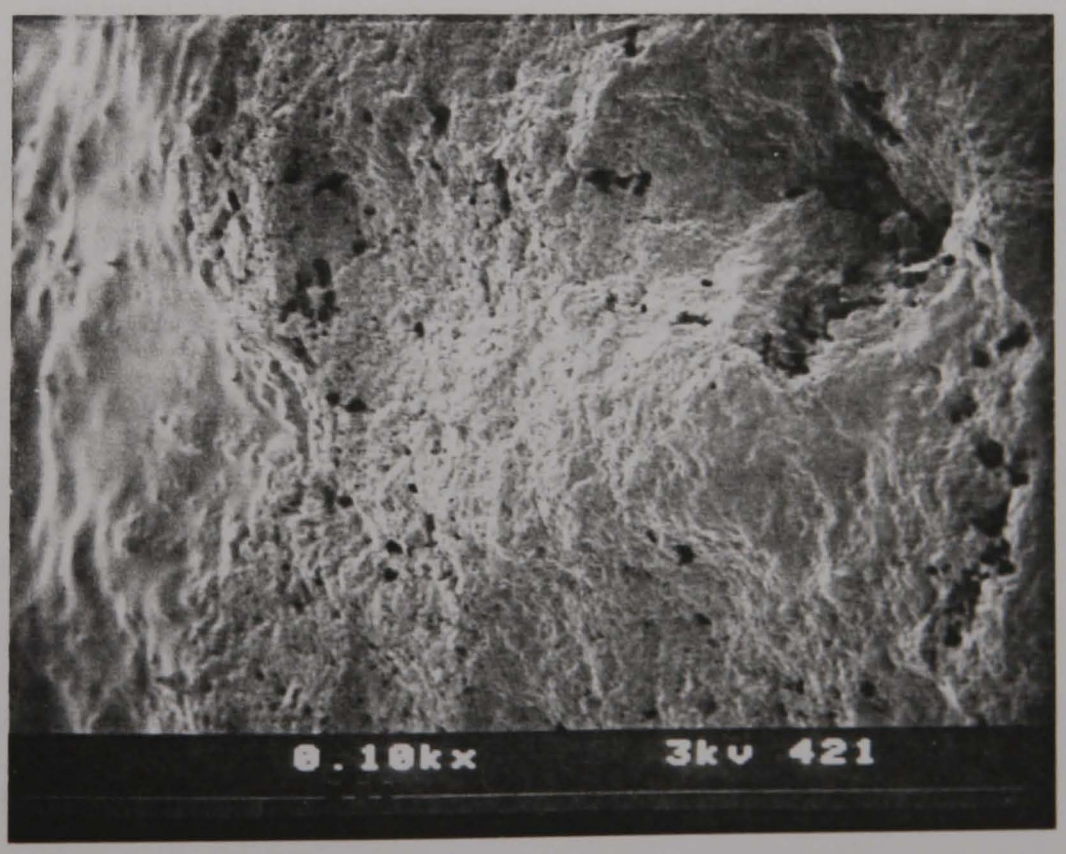


Figure 7.19. SEM of the surface of a pellet coated with ERS/RL30D after release from a tablet matrix; magnification x400

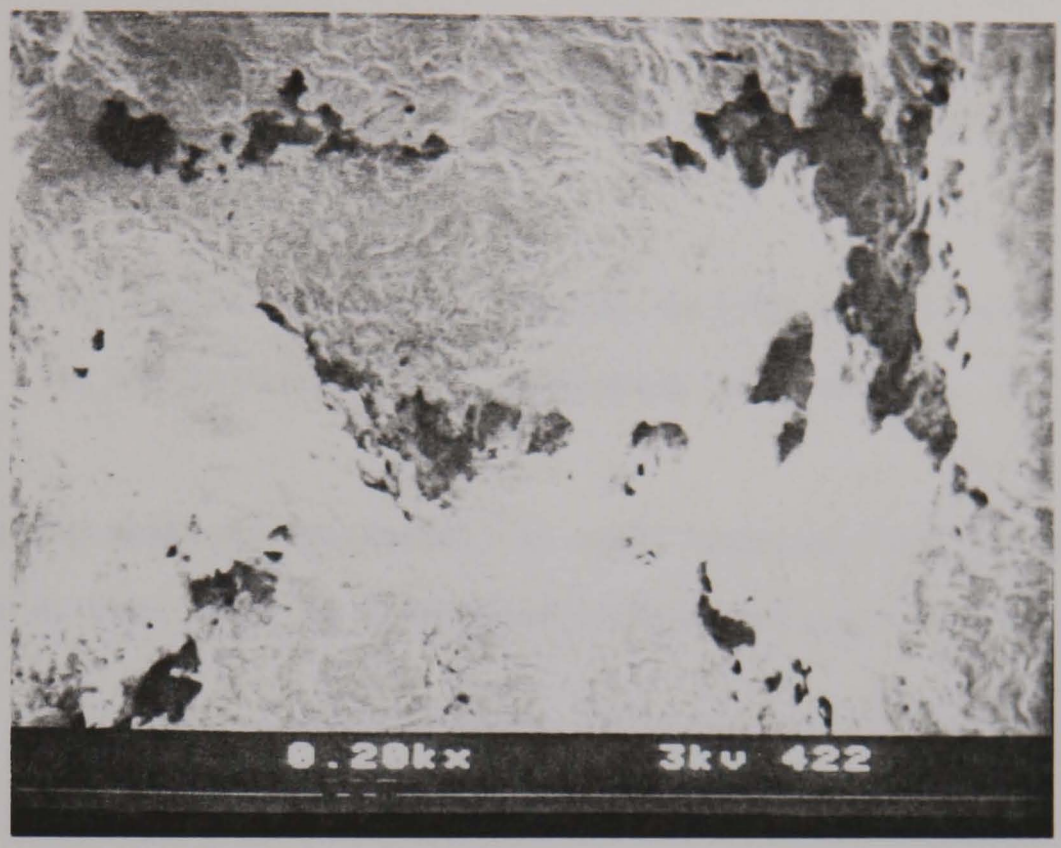


Figure 7.20. SEM of the surface of a pellet coated with ERS/RL30D after release from a tablet matrix; magnification x800

7.3.4. Mathematical interpretation.

7.3.4.1. Calculation of Hoop Stress.

The application of external pressure to a polymer coated pellet during compression causes a tensile stress to be established within the surrounding polymeric membrane due to the tendency of the sphere to deform under pressure. This tangential stress is dissipated within the membrane shell until the applied pressure is so great as to cause pellet fracture.

The thin-walled spherical particle is subjected to an external pressure p which induces in the film coat a circumferential stress σ which has the same value in all tangential directions and is assumed to be constant over membrane thickness t. Considering the cross-section of a sphere surrounded by a membrane, the forces acting on one half of the pellet are two fold:

i). the diametral force due to the applied pressure p

$$= \text{pressure x cross-sectional area} = p\frac{\pi d^2}{4} \qquad \text{Equation 7.1.}$$

ii). the resisting force due to the circumferential stress σ, acting on the section of the surrounding membrane.

Assuming the membrane thickness t is small compared with the particle diameter d, then σ may be considered uniform and therefore the resisting force

$$= \text{stress x area of film} = \sigma\pi dt \qquad \text{Equation 7.2.}$$

Equating these two forces and rearranging enables calculation of the tangential stress:

$$\sigma\pi dt = p\frac{\pi d^2}{4} \qquad \text{Equation 7.3.}$$

Therefore the tangential (hoop) stress

$$\sigma = \frac{pd}{4t} = \frac{pr}{2t} \qquad \text{Equation 7.4.}$$

where r is the particle radius.

In summary the tangential (hoop) stress associated with the polymeric membrane surrounding a spherical particle, is directly proportional to the external pressure applied and the diameter of the particle; it is inversely proportional to the thickness of the surrounding membrane.

7.3.4.2. Calculation of Volumetric Strain.

Assuming the diameter of the polymer coated sphere decreases by an amount δd when the external pressure is increased from zero to p as a consequence of pellet compression, then the volumetric strain ϵ_v

$$\epsilon_v = \frac{\text{final volume - original volume}}{\text{original volume}} \qquad \text{Equation 7.5.}$$

$$\epsilon_v = \frac{\text{final volume}}{\text{original volume}} - 1 \qquad \text{Equation 7.6.}$$

$$\epsilon_v = \frac{(\pi/6)(d - \delta d)^3}{(\pi/6)d^3} - 1 \qquad \text{Equation 7.7.}$$

$$\epsilon_v = \frac{d^3 - 3d^2\delta d - 3d\,\delta d^2 - \delta d^3}{d^3} - 1 \qquad \text{Equation 7.8.}$$

(ignoring products of small terms)

$$\epsilon_v = 1 - 3\frac{d^2\,\delta d}{d^3} - 1 \qquad \text{Equation 7.9.}$$

$$\epsilon_v = -3\frac{\delta d}{d} \qquad \text{Equation 7.10.}$$

i.e. the volumetric strain = - 3 x diametral strain

= - 3 x circumferential strain

where the volumetric strain ϵ_v, may be defined as the change in volume per unit volume.

Therefore the volumetric strain

$$\epsilon_v = -\frac{3\sigma}{E} \qquad \text{Equation 7.11.}$$

where E is the modulus of elasticity, therefore the volumetric strain

$$\epsilon_v = -\frac{3pd}{4tE} \qquad \text{Equation 7.12.}$$

since $\sigma = pd/4t$ (Equation 7.4).

7.3.4.3. Change in particle volume.

The change in volume of the sphere (δV) equals ϵ_v x original volume i.e.

$$\delta V = -\frac{3pd}{4tE} \cdot \frac{\pi d^3}{6} \qquad \text{Equation 7.13.}$$

$$\delta V = -\frac{\pi p d^4}{8tE} \qquad \text{Equation 7.14.}$$

(the change in particle volume is negative representing a volume decrease with applied external pressure).

The above theory assumes that the pellet core itself does not contribute to that force resisting the application of pressure due to pellet compression; this however is not the case.

7.3.5. Practical application.

7.3.5.1. Determination of the hoop stress of an applied film.

In order to quantify that hoop stress associated with the application of force to a coated particle, it is necessary to determine that stress associated with the pellet core. By considering the stress of an uncoated pellet on the application of load just prior to fracture and comparing this with that associated with a coated entity, it is possible to quantify that hoop stress provided by the physical presence of the film coat.

Consider an uncoated ibuprofen pellet containing 80%w/w drug (expressed as % weight dry solids) of particle diameter 1107μm exhibiting a diametral crushing strength of 2.59N, a stress of 2.72MPa and a strain of 0.0779 (data extracted from Table 6.5). Since this particle is without film coat, the entire force is absorbed by the pellet core; this is reflected in a particle stress of 2.72MPa.

In contrast to this a particle coated with polymeric membrane to a pellet weight increase of 4.5%, has a mean diameter of 1145μm and exhibits a crushing force of 2.74N, a stress of 2.66MPa and strain of 0.0781. In addition to this a particle coated with a polymer film of weight increase 12% has a mean diameter of 1144μm and exhibits a crushing force of 2.81N, a stress of 2.74MPa and strain of 0.0825 (data extracted from Table 6.5).

Considering pellets coated with the 4.5% weight increase: the film thickness t is (1145 - 1107)/2, equivalent to 19μm. Substituting in Equation 7.4 therefore, by considering that additional force required to fracture a coated pellet when compared to the pellet core, the hoop stress $\sigma = pd/4t = pr/2t$ and $p = F/A$, where F is the force for fracture and A is the cross-sectional area.

Therefore the hoop stress of a membrane associated with a 4.5% weight increase

$$= \frac{[(2.74 - 2.59)/\pi r^2] \text{ x } 1.107}{4 \text{ x } 0.019} = 2.27 \text{ MPa}$$

For a 12% polymer solids loading, the hoop stress associated with the presence of the film

$$= \frac{[(2.81 - 2.59)/\pi r^2] \text{ x } 1.107}{4 \text{ x } 0.0185} = 3.42 \text{ MPa}$$

This appears to indicate that for ibuprofen pellets coated with a 4.5% weight increase, it is the weakness of the film which enables pellet fracture since the uncoated pellet is able to withstand a greater stress (2.66MPa) than the polymeric film (2.27MPa).

For a 12% weight increase however the film is able to withstand a greater stress (3.42MPa) than the uncoated pellet (2.66MPa) and it is the relative weakness of the pellet core which facilitates pellet fracture under applied load.

The ability of the pellet core and film coating in combination to withstand stress is related to the particle diameter in addition to the diametral crushing strength. Therefore it is not unreasonable that there is a reduction in the stress associated with a pellet coated with a 4.5%w/w solids increase, since the particle size is increased. It is apparent that further application of solids to the pellets (to 12%w/w) does not result in an increase in the pellet diameter; this may be explained by the fact that the additional weight gain is associated with bridging of "gaps" within the newly formed film itself. *In-vitro* release profiles support this postulation (Figure 4.7) since the drug release

rate is time dependent (first-order) at low polymer loading (4.5%w/w) but becomes time independent at higher polymer levels (12%w/w).

The underlying theory in support of this claim is that under conditions of low polymer loading (below the CCL) drug release is pore controlled, whilst above the CCL drug release appears to exhibit barrier-controlled or zero-order kinetics. It is postulated that a polymeric film is created by a build-up of continuous layers of overlapping segments and until all of the "holes" associated with this gradual build-up are covered and a complete membrane envelopes each individual pellet there will be imperfections and areas of incomplete coverage of individual pellets.

An effect of coating pellets with a polymeric film results in enhanced pellet deformability under stress and an increase in the work required to cause pellet fracture. The strain exhibited by pellets is also increased (Table 6.5).

7.3.5.2. Calculation of volumetric strain.

The volumetric strain exhibited by the polymer film may be calculated using Equation 7.12. Therefore with polymer loading of 4.5%w/w

$$\epsilon_v = - \frac{3 \text{ x } [(2.74 - 2.59)/\pi r^2] \text{ x } 1.107}{4 \text{ x } 0.019 \text{ x } E}$$

E for the polymer film = 30.55MPa, and therefore ϵ_v = - 0.223.

With a polymer loading of 12%w/w the volumetric strain

$$\epsilon_v = - \frac{3 \text{ x } [(2.81 - 2.59)/\pi r^2] \text{ x } 1.107}{4 \text{ x } 0.0185 \text{ x } E}$$

and ϵ_v = - 0.336.

Strain is an expression of the elastic deformation of a particle and expresses the relative change in dimension in the direction of the applied force. Since the volumetric strain is equivalent to thrice the diametral strain, the theoretical diametral strain exhibited by the polymeric membrane at 4.5 and 12% weight increase is equal to 0.074 and 0.112 respectively (c.f. strain exhibited by the coated pellets of 0.0781 and 0.0825 respectively). The strain exhibited by a similar uncoated particle is 0.079 and it therefore appears that the strain exhibited by a polymeric film increases with increasing physical strength for a given particle size.

The following table shows the relative elastic moduli *E* of the uncoated pellet formulation containing 80%w/w ibuprofen, the coated pellets and the polymer itself; the data source is quoted accordingly.

Product	*E* (MPa)	Source
uncoated pellet	34.92	Table 6.5
coated pellet (4.5%)	34.06	Table 6.5
coated pellet (12%)	33.21	Table 6.5
ERS/RL free-film	30.55	Table 5.5

Table 7.12. Summary of experimentally determined elastic moduli values *E* (MPa) for the pellet component products.

It is apparent that the elasticity of the optimised polymeric film formulation is not significantly different from that displayed by uncoated pellets. The effect of applying a polymeric film to an uncoated pellet formulation is increased elasticity with increased polymer loading. The success of the formulation in respect of pellet coat, core integrity and compression is thought to be a consequence of the not dissimilar elastic properties of the uncoated pellet and the free-film

formulations. This particular Eudragit formulation most closely mimicked the elastic behaviour of the uncoated pellets (see Tables 5.5 to 5.14). Those films exhibiting relatively low elastic modulus values (ie. were more elastic) for example the Silicone Elastomer free-films, with values as low as 5.0MPa, were as previously discussed non-compressible due to instantaneous elastic recovery on removal of the applied load.

7.3.5.3. Change in particle volume.

The change in particle volume may be calculated using Equation 7.14:

$$\delta V = - \frac{\pi p d^4}{8tE}$$

Therefore for ibuprofen pellets coated with 4.5% and 12% weight increases respectively, the maximum change in pellet volume $\delta V = - 0.158mm^3$ and $- 0.239mm^3$ respectively; the change in volume is negative representing a decrease in particle volume with applied external pressure.

The minimum volume V_f a coated particle will contract to just prior to fracture on the application of stress may be calculated using the following equation:

$$V_f = \frac{V_o - \delta V}{V_o} \times 100 \qquad \text{Equation 7.15.}$$

where V_o is the original volume of the coated sphere prior to the application of stress. The volume of a spherical particle = $4/3\pi r^3$, where the coated particle radius must now taken into consideration; the coated particle volume therefore = $0.786mm^3$.

Using the above examples therefore the V_f values are 79.9% and 69.6% respectively; a pellet coated with a 4.5% weight increase may occupy a minimum volume of approximately 80% of that of its original volume under

applied load and a pellet coated with a 12% weight increase may occupy as little as approximately 70% of its original volume under applied load.

7.4. Conclusions.

The aim of this work was to design a monolithic delivery device for a model medium to high dose drug which on oral administration rapidly disintegrates releasing polymer coated sustained release pellets, with the integrity of the pellet core and the polymeric membrane being maintained.

It is apparent that with careful optimisation of the pellet core, the film coat and the inert diluent formulations, it is possible to present a rapidly disintegrating monolithic sustained release drug delivery system for oral administration comprising compacted polymer-coated pellets.

The optimised diluent blend formulation comprises 40%w/w of the tablet matrix; the remaining 60%w/w being occupied by the coated pellets. Large particle size excipients appear to provide the most satisfactory product. In the quest to achieve a rapidly disintegrating tablet which is able to satisfy the requirements of the friability test, it was necessary to use a blend of microcrystalline cellulose and lactose to impart properties characteristic of the combined components. It was not possible to produce strong, rapidly disintegrating tablets with lactose alone forming the tablet matrix, but in combination with microcrystalline cellulose the resulting tablets exhibit desirable diametral strength and rapid disintegration.

The aqueous polymeric dispersion which formed a film displaying similar elastic and tensile properties to the uncoated pellet formulation, resulted in the most satisfactory film coating for application to spherical particles which must withstand compaction. Those polymeric films exhibiting significantly greater elasticity than

the uncoated pellet cores were inappropriate for film coating pellets which were to be compacted into tablets. This was due to the tendency of these films to exhibit instantaneous elastic recovery on the removal of the load associated with compaction, such that even maximum compaction forces were not capable of producing cohesive tablets containing these polymer coated entities.

Pellets are rapidly released from the matrix on disintegration of the tablet. Released pellets are visibly intact although there is evidence of a deleterious effect on the smoothness of the surface and the quality of the shape of the spheres (Figures 7.8 and 7.9). *In-vitro* release profiles for compacted pellet formulations at different compaction forces and for non-compacted entities do indicate that some physical damage is being caused to at least some of the multiparticulates. The extent of the damage however does not appear to be dependent upon the magnitude of the compaction force (Figures 7.5 and 7.6), but upon the actual process of compaction. The minimum force necessary to enable the formation of a tablet which will satisfy the friability testing requirements resulted in pellet damage of a similar extent to that displayed by tablets compressed with a significantly greater compaction force and which exhibit a correspondingly greater diametral strength.

Microphotographs of stained pellets have illustrated that pellet distribution appears to be uniform throughout the tablet matrix. Quantitative evaluation of pellet distribution within the compacted formulation using image analysis however appears to indicate that pellets are randomly distributed. Uniformity of weight, uniformity of content and *in-vitro* drug release data however shows that under these conditions there is little tendency for particle segregation. It is accepted that this may be not be the case on scaling up the operation however.

Evidence suggests that those pellets most susceptible to physical

damage as a consequence of the compaction process appear to occur at the tablet surface. Those pellets making contact with the tablet punches during compaction are not buffered to the same extent by the diluent particles as those not forming a tablet surface. Pellets forming an integral part of the tablet surface exhibit severe deformities which are manifest as linear edges and sharp corners; these are visible both in tablet cross-sections composed of stained pellets (Figure 7.16) and on pellets which have been released from the tablet matrix by disintegration (Figures 7.8 and 7.9).

Scanning electron micrographs have illustrated the nature of the type of damage to pellets which may occur as a consequence of compaction into tablets (Figures 7.18 to 7.20).

The hoop stress associated with the physical presence of a polymeric membrane surrounding a pellet core is capable of enhancing the diametral strength of a coated pellet, providing that sufficient polymer is applied. Increasing the amount of film coating solids applied to pellets has the effect of enhancing the physical strength, the elasticity (reflected in a reduction of the elastic modulus of pellets with increased polymer loading) and the deformability or strain exhibited by the particle under load and for a given particle size; there is also an increase in the stress the particle will withstand prior to fracture.

The application of external pressure to a particle causes a tensile stress to be established within the polymeric membrane and the pellet core, due to the tendency of the pellet to contract. Mathematically it has been shown that the volumetric strain a particle will exhibit is three times the diametral strain. This has been applied in a practical situation to coated pellets and gives an insight into the effect of the physical presence of a polymer coating on the particle deformability.

In summary, this work has shown qualitatively and quantitatively that with careful optimisation of formulation variables, it is possible

to present a rapidly disintegrating monolithic sustained release drug delivery system for oral administration comprising compacted polymer-coated pellets. In order to minimise physically damaging multiparticulates as a consequence of compaction, it is prudent to ascertain and understand the physical and mechanical properties of the components of the dosage form and to utilise this information to generate a product in which the benefits of this investigative research may be applied.

CHAPTER 8

FINAL SUMMARY

An oral sustained release drug delivery system comprising compacted polymer-coated pellets confers pharmacological and pharmaceutical advantages associated with the administration of a once daily product. A sustained release multiparticulate dosage form which rapidly releases intact sub-units on oral administration improves patient compliance as a result of reduced frequency of dosing, reduced fluctuations in plasma drug concentrations and greater predictability and reproducibility of the therapeutic effect.

This work has incorporated a study of formulation and processing variables of pellets prepared by extrusion and spheronisation and their effect on the physical and release properties of uncoated pellets. Furthermore elucidation of the tensile properties of free-films prepared from aqueous polymeric dispersions and a study of the effect of the physical presence of a polymeric membrane on the tensile properties of coated pellets has enabled the presentation of polymer coated multiple-units as a rapidly disintegrating single-unit drug delivery system for a low potency drug.

Those variable parameters influencing the physical characteristics of uncoated pellets are indeed numerous and are well documented. This work however has revealed that the drying methodology used and consequently the rate of the drying process for pelletized material has a significant effect on the skeletal, tensile and release properties of uncoated pellets containing ibuprofen. Pellets dried by tray drying exhibit greater diametral strength, are less elastic and display a slightly enhanced rate of drug release compared with their fluidised bed dried counterparts.

The drying technique also imposes its effect upon the surface characteristics and quality of uncoated pellets prepared using this technique. Pellets dried rapidly using a fluidised bed apparatus are smoother with more uniform surface characteristics than tray dried

entities. Fluidised bed dried pellets therefore lend themselves more favourably to the application of a release retarding polymeric membrane due to the excellent surface smoothness which is evident with particles dried in this manner.

The aqueous solubility of the excipients of the uncoated pellet formulation influences the type of bonding which is responsible for the maintenance of pellet integrity. Excipients which are freely soluble in the granulating fluid appear to be more susceptible to the phenomena of solute migration during drying. Where the granulating fluid is aqueous and the excipients are freely water soluble, crystallisation of the solute molecules during drying leads to the formation of solid bridges and particles of great diametral strength. Where the main excipient exhibits poor aqueous solubility as does ibuprofen, the pellets are largely held together by binder hardening during drying. Increasing the binder concentration of the uncoated pellets therefore has the effect of enhancing the particle strength and reducing particle elasticity.

A prerequisite of complete film formation and polymer coalescence for aqueous polymeric dispersions, in addition to optimised processing variables, is a reduction in the minimum film forming temperature (MFT) to well below the operating conditions of the coating chamber. Providing this is achieved it does not appear to be necessary to subject polymer coated pellets to a post-coating "curing" stage following that drying facility provided by the film coating operation. This is illustrated by the negligible difference in the *in-vitro* release profiles of pellets subjected to the post-coating "curing" stage and those which were not.

A study of the tensile properties of free-films and polymer-coated pellets was made in order to ascertain that polymeric film formulation which was best able to sustain the effect of the applied stress associated with pellet compaction. A search for those physical properties responsible for providing that combination of strength and

elasticity was made and this enabled the compaction of pellets with minimum particle damage. Qualitative film evaluation was made possible using microphotography and scanning electron microscopy and quantitative film evaluation was performed using *in-vitro* dissolution testing.

An analysis of elastic and plastic deformation of polymer films was provided using the technique of indentation hardness testing of free-films. Quantifiable parameters using this technique included the instantaneous and time-dependent elastic deformation and recovery of the films, the elastic modulus and the Newtonian viscosity. An effect of increasing the plasticiser content of a particular film formulation serves to increase the instantaneous and time-dependent elastic components and cause a reduction in the elastic modulus and the apparent Newtonian viscosity. In general the permanent non-recoverable plastic deformation associated with applied stress, increases with increasing plasticiser concentration.

The presence of other excipients within a film may also exert an influence on the resultant tensile properties. This effect is however product specific.

It is evident from studying the tensile properties of free-films that those polymeric films exhibiting a high elastic compliance, both instantaneous and time-dependent, are unlikely to satisfy the requirements for favourable pellet compaction, due to elastic recovery occurring immediately on removal of the applied stress associated with tablet compression. It is apparent from this work that those films exhibiting a relatively high elastic modulus and apparent Newtonian viscosity provide greater protection to the integrity of the pellet core and the film coat on pellet compression.

The predominant drug release mechanism from polymer coated pellets is a function of polymer loading. There appears to be a critical coating level below which film coverage may be considered incomplete, drug

release is diffusion controlled and first-order kinetics are observed. Above this critical coating level, drug release appears to become membrane controlled and zero-order kinetics are evident. The drug release rate appears to become time independent once a certain polymer level has been achieved.

With careful optimisation of the pellet core formulation and processing technique, the film coating and the inert diluent blend, it is possible to present a rapidly disintegrating sustained release tablet matrix suitable for oral administration, comprising polymer coated multiparticulates.

The magnitude of the compaction force on the extent of particle damage appears to be of little consequence. Rather that the actual process of compaction as opposed to the magnitude of the load applied to the pellets appears to be responsible for any damage which is caused to particles during compression. The minimum compaction force necessary for tablet formation which enables tablets to fulfill the requirements of friability test, results in similar damage to that caused to pellets compacted with a far greater force with a corresponding diametral strength. In addition to microphotographic evidence, this suggests that those pellets most susceptible to damage as a consequence of compaction are at the tablet surface. Those pellets forming the surface are not buffered by surrounding diluent particles from contact with the tablet punches. In particular those particles forming a tablet surface are especially vulnerable to impaired integrity and may exhibit severe deformities in the form of sharp corners and linear edges, which it is postulated are responsible for the slightly increased rate of drug release which is apparent with the compacted pellet formulation (Figure 8.1). The magnitude of pellet damage was assessed by scanning electron microscopy of the film coat following pellet compaction and by comparison of the *in-vitro* release profiles of compacted and non-compacted pellets.

Figure 8.1a. Microphotograph of the cross-section of a tablet comprising compacted stained pellets; magnification x20.

Figure 8.1b. Microphotograph of the cross-section of a tablet comprising compacted stained pellets; magnification x20.

Image analysis of tablet sections comprising stained pellets enabled a study of pellet distribution within the tablet matrix and the inclination of the components of the blend towards particle segregation. Image analysis, microphotography and uniformity of weight and content data present negligible evidence of segregation.

Further development work might involve a scaling-up of this concept in order that a full investigation into the tendency of the components of the tablet blend to undergo particle segregation may be ascertained. Although in this study ibuprofen was used as a model high dose or low potency drug, it would be interesting to apply this technique to other drugs of differing aqueous solubility and physicochemical properties. It is clear that the diametral strength and tensile properties of uncoated pellets are very much dependent upon processing variables and formulation factors and therefore the use of different compounds would yield additional fundamental data relating to other excipients in respect of the tensile properties of pellets prepared using these techniques.

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APPENDIX

APPENDIX I

Principle of operation of the Multivolume Pycnometer.

The Micromeritics Multivolume Helium Pycnometer 1305 is a gas displacement pycnometer, which measures the volume of solids whether powdered or as single entities. Figure 2.4 is a simplified illustration of the principle behind the apparatus.

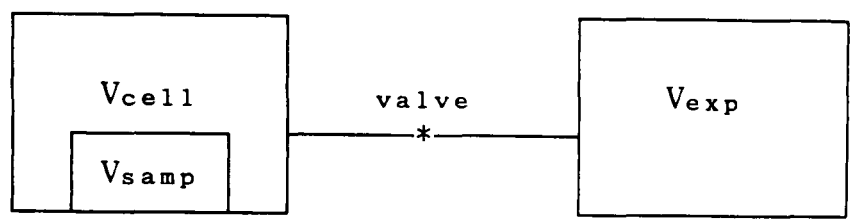

Figure 2.4. Simplified block diagram of Helium Pycnometer 1305.

where V_{cell} = calibrated sample cell volume

V_{samp} = sample volume

and V_{exp} = calibrated expansion volume.

Assuming that V_{cell} and V_{exp} are at ambient pressure P_a and temperature T_a and that the valve is closed, then if V_{cell} is charged to an elevated pressure P_1, then the mass balance equation across the sample V_{cell} is

$$P_1 (V_{cell} - V_{samp}) = n_c R T_a \qquad \text{Equation 2.1}$$

where n_c = number of moles of gas in the sample cell

R = gas constant

and T_a = ambient temperature.

The mass equation for the expansion volume is

$$P_a V_{exp} = n_e R T_a \qquad \text{Equation 2.2}$$

where n_e = number of moles of gas in the expansion volume.

When the valve is opened, the pressure will fall to an intermediate value P_2 and the mass balance equation becomes

$$P_2 (V_{cell} - V_{samp} + V_{exp}) = n_c R T_a + n_e R T_a \qquad \text{Equation 2.3}$$

Substituting from equations 2.1 and 2.2 into 2.3

$$P_2 (V_{cell} - V_{samp} + V_{exp}) = P_1 (V_{cell} - V_{samp}) + P_a V_{exp} \qquad \text{Equation 2.4}$$

rearranging

$$P_2V_{cell} - P_2V_{samp} + P_2V_{exp} = P_1V_{cell} - P_1V_{samp} + P_aV_{exp}$$

$$\equiv P_2V_{cell} - P_2V_{samp} = P_1V_{cell} - P_1V_{samp} + P_aV_{exp} - P_2V_{exp}$$

$$\equiv P_2V_{cell} - P_2V_{samp} = P_1V_{cell} - P_1V_{samp} + (P_a - P_2)V_{exp}$$

$$\equiv P_2V_{cell} - P_2V_{samp} - P_1V_{cell} + P_1V_{samp} = (P_a - P_2)V_{exp}$$

$$\equiv (P_2 - P_1) (V_{cell} - V_{samp}) = (P_a - P_2) V_{exp} \qquad \text{Equation 2.5}$$

or

$$V_{cell} - V_{samp} = \frac{(P_a - P_2) V_{exp}}{P_2 - P_1} \qquad \text{Equation 2.6}$$

rearranging

$$- V_{samp} = - V_{cell} + \frac{(P_a - P_2) V_{exp}}{(P_2 - P_a) - (P_1 - P_a)} \qquad \text{Equation 2.7}$$

dividing by $(P_a - P_2)$

$$V_{samp} = V_{cell} - \frac{V_{exp}}{-1 - \frac{(P_1 - P_a)}{(P_a - P_2)}} \qquad \text{Equation 2.8}$$

or

$$V_{samp} = V_{cell} - \frac{V_{exp}}{\frac{(P_1 - P_a)}{(P_2 - P_a)} - 1} \qquad \text{Equation 2.9}$$

Since P_1, P_2 and P_a are expressed in equations 2.1 to 2.9 as absolute pressures, and equation 2.9 is arranged such that P_a is subtracted from both P_1 and P_2 before use, new P_{1g} and P_{2g} may be redefined as gauge pressures

$$P_{1g} = P_1 - P_a \qquad \text{Equation 2.10}$$

$$P_{2g} = P_2 - P_a \qquad \text{Equation 2.11}$$

therefore equation 2.9 becomes

$$V_{samp} = V_{cell} - \frac{V_{exp}}{\frac{P_{1g}}{P_{2g}} - 1} \qquad \text{Equation 2.12}$$

Equation 2.12 is the working equation for the Multivolume Pycnometer 1305. Calibration procedures using a steel sphere of precise dimensions enabled determination of V_{cell} and V_{exp}. P_1 and P_2 were measured by means of a gauge pressure transducer.

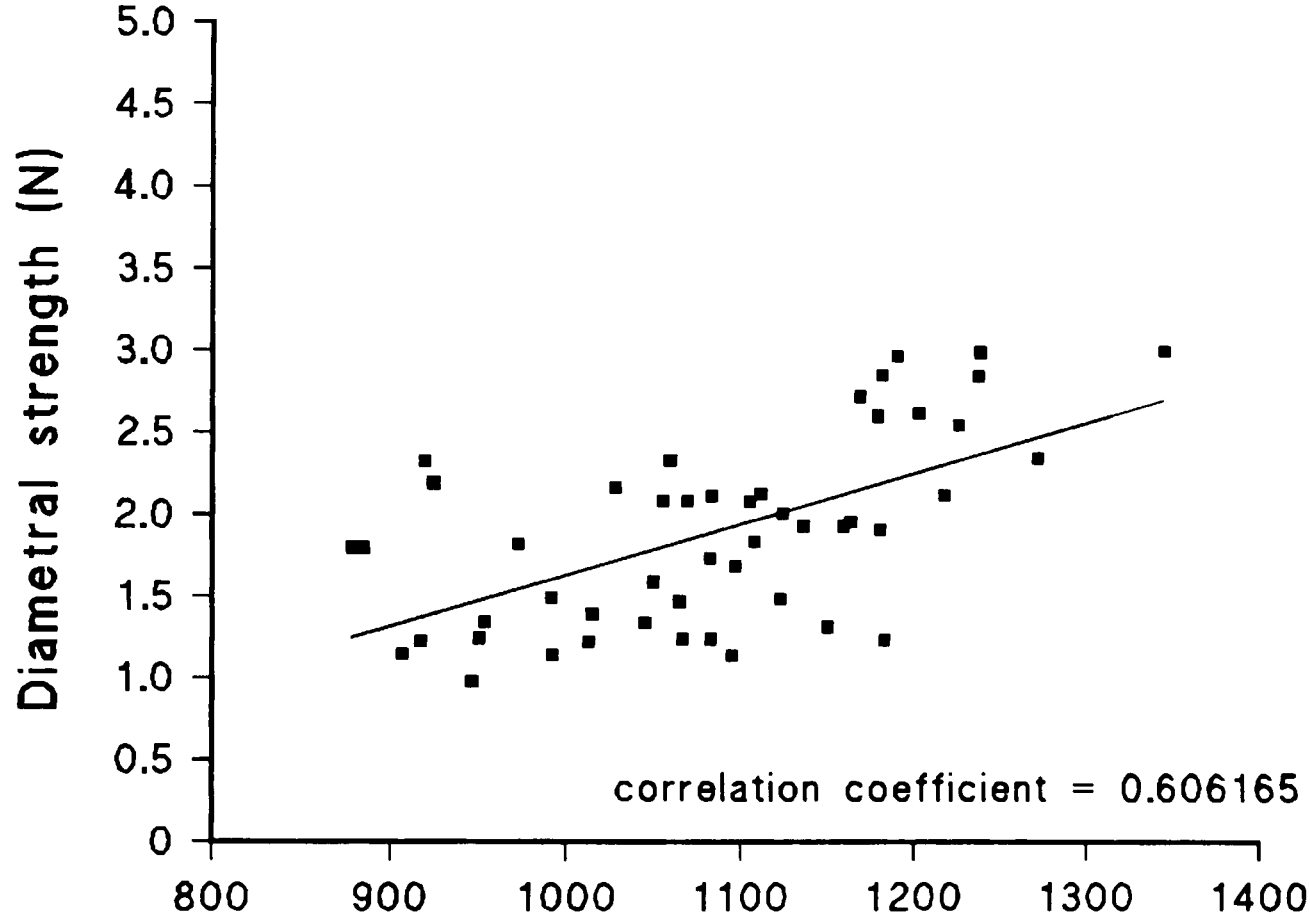

Figure 6.20. Linear regression plot of pellet diameter (μm) versus diametral strength (N) for fluidised bed dried pellets containing 80%w/w ibuprofen (uncoated).

Curve statistics:

X-data: mean pellet diameter = 1083.51μm
SD = 109.18μm

Y-data: mean diametral strength = 1.910N
SD = 0.579N

Curve-fit: (y) = 0.003215(x) - 1.5738

n = 49